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STUDIES TOWARD THE TOTAL SYNTHESIS OF SALIMABROMIDE VIA DEAROMATIZATION OF 1-NAPHTHOLS

AND

INVESTIGATION OF THE CLAISEN REARRANGEMENT OF ALLYL CHLOROVINYL ETHERS

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Eidesstattliche Versicherung

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TO MY FAMILY

Parts of this work have been published in peer-reviewed journals:

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"Rapid Access to Orthogonally Functionalized Naphthalenes: Application to the Total Synthesis of the Anticancer Agent Chartarin" T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chem., Int. Ed.* **2016**, *55*, 9763–9767. (HOT PAPER)

"*Ring Opening of Bicyclic[3.1.0]hexan-2-ones: A Versatile Synthetic Platform for the Construction of Substituted Benzoates*" J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem., Int. Ed.* **2015**, *54*, 11835–11838.

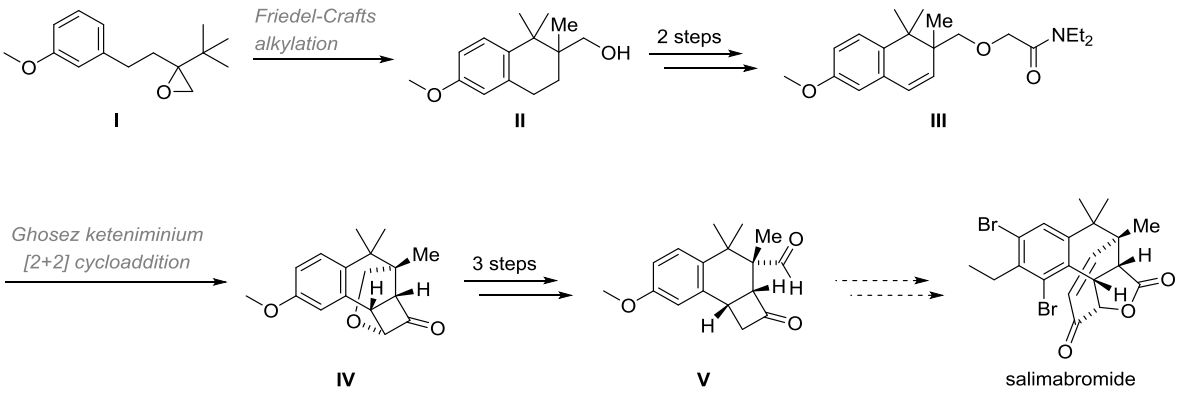
ABSTRACT

CHAPTER I:

STUDIES TOWARD THE TOTAL SYNTHESIS OF SALIMABROMIDE

In 2013, one of the first examples of a secondary metabolite from an obligate marine myxobacterium was reported. The halogenated polyketide salimabromide was isolated from *Enhygromyxa salina* and consists of an unprecedented tetracyclic core structure featuring a dibrominated benzene ring. It contains four consecutive stereogenic centers, one of which is an all carbon quaternary center. Moreover, this chiral quaternary center resides adjacent to an additional all carbon quaternary carbon.

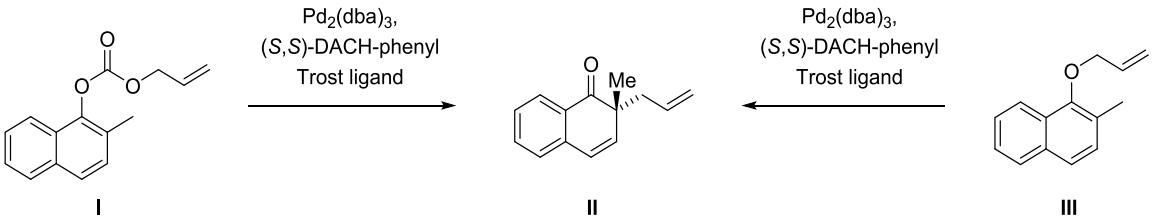
The first part of this thesis describes synthetic efforts toward the synthesis of salimabromide. Both the tetraline core and the quaternary centers were successfully installed in a single step using an intramolecular Friedel-Crafts alkylation (**I** → **II**). The amide precursor **III** for the key step – a keteniminium [2+2] cycloaddtion developed by Ghosez – was synthesized in two further steps. Successful application of the Ghosez method in our synthesis allowed the creation of three additional stereocenters in a single process and in a stereodefined manner. Therefore, the single stereocenter of the tetralin core of **II** could be used to stereoselectively install all the others present in salimabromide. The highly congested tetracyclic intermediate **IV** was then converted in three subsequent steps to tricyclic aldehyde **V**, the precursor for the Aldol condensation to close the cycloheptenone portion of the natural product.



CHAPTER II:

CATALYTIC ASYMMETRIC DEAROMATIZATION (CADA) REACTIONS

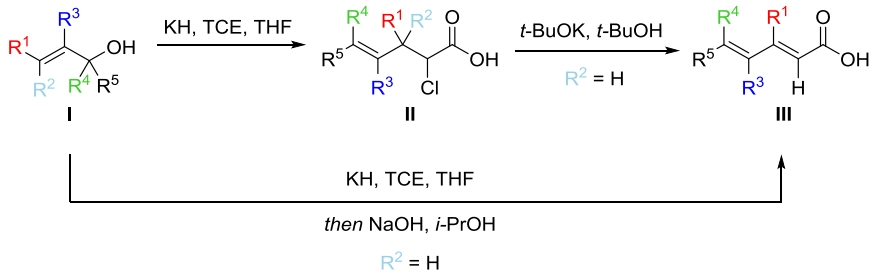
The asymmetric synthesis of all carbon quaternary centers is a challenging problem for synthetic chemists. In the second part of this thesis, the development of an intramolecular CADA reaction of 2-substituted 1-naphthols is described. We were able to overcome the challenge of rearomatization via subsequent Cope rearrangement by developing mild and neutral conditions. Diallylation caused by ion diffusion was avoided by the use of more elaborated chiral ligands. In general, two types of substrates were found to be suitable for this CADA reaction of 1-naphthols: allyl carbonates **I** and allyl ethers **III**. Heating the substrates in benzene to 45 °C in the presence of 5 mol% Pd_2dba_3 and 11 mol% of a chiral ligand afforded 3,4-dehydro-1-tetralone **II** in up to 84% yield. Amongst several chiral ligands screened, the (*S*,*S*)-DACH-phenyl Trost ligand appeared to give the highest yields and *ee* values of around 59%. Higher *ee* values could be obtained with the (*S*,*S*)-DACH-naphthyl Trost ligand, which gave constantly values around 70%, although the yields were moderate. Several substrates with different substituents were treated with these conditions to afford the corresponding ketones in very good yields.



CHAPTER III:

CLAISEN REARRANGEMENT OF ALLYL CHLOROVINYL ETHERS

The third chapter of this thesis presents the development of a synthetic methodology to afford α-chlorinated acids **II** and 2,4-dienoic acids **III** from allylic alcohols **I**. For the synthesis of α-chlorinated acids **II** commercially available allylic alcohols were treated with KH and trichloroethene (TCE) at low temperatures to undergo an elimination-addition reaction and form 1,2-dichlorovinyl ether at around −30 °C. Upon warming to −10 °C, the ethers undergo in situ Claisen rearrangement to generate α-chlorinated acid chlorides which are hydrolyzed upon work-up. The obtained products were heated under basic conditions to 85 °C to formally eliminate HCl and obtain the corresponding dienoic acids **III**. A one-pot protocol for this reaction sequence was established as well. However, the sensitivity of both types of products **II** and **III** toward a variety of purification methods made their isolation and identification very difficult. Furthermore, the generation of the α-chlorinated acids was problematic and often resulted in low yields.



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LIST OF ABBREVIATIONS

Å	Ångstrom
AADA	asymmetric allylic dearomatization
Ac	acetyl
acac	acetlyacetone
AIBN	azobisisobutyronitrile
ANDEN	(+)-(11*S*,12*S*)bis[2'-(diphenyl phosphino)benzamido]-9,10-dihydro-9,10-ethanoanthracene
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BPO	bromoperoxidase
br	broad (NMR spectroscopy, IR spectroscopy)
Bu	butyl
CADA	catalytic asymmetric dearomatization
calcd	calculated
CoA	Coenzyme A
cod	1,5-cyclooctadiene
COSY	homonuclear correlation spectroscopy
CPME	cyclopentyl methyl ether
CPO	chloroperoxidase
d	doublet (NMR spectroscopy); day(s)
dr	diastereomeric ratio
DACH	1,2-diaminocyclohexane-*N*,*N*'-bis(2-diphenylphosphino benzoyl)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	tris(dibenzylideneacetone)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCA	dichloroacetylene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-4,5-dicyano-1,3-benzoquinone
DEG	diethylene glycol
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMC	dimethyl carbonate
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
dmdba	3,5,3',5'-dimethoxy-dibenzylideneacetone
DMSO	diemethylsulfoxide
d.r.	diastereomeric ratio
dppe	1,2-bis(diphenylphosphino) ethane
dppf	1,1'-bis(diphenyl-phosphino)ferrocene
E^0	reduction potential
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
EI	electron impact ionization (mass spectrometry)
equiv	equivalent(s)

ESI	electron spray ionization (mass spectrometry)
Et	ethyl
EWG	electron withdrawing group
FAD	flavin adenine dinucleotide
FDA	food and drug administration
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
h	hour(s)
HFIP	hexafluoro-2-propanol
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation
HMDS	bis(trimethylsilyl) amide
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HPO	haloperoxidase
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i-	*iso*
IC_{50}	half maximal inhibitory concentration
im	imidazole
IR	infrared spectroscopy
J	coupling constant (NMR spectroscopy)
LDA	lithium diisopropylamide
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
m-CPBA	*meta*-chloroperbenzoic acid
MDA	methyl dichloroacetate
Me	methyl
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MS	mass spectrometry
MTBE	methyl-*tert*-butylether
NBS	*N*-bromosuccinimide
NCI	national cancer institute
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine *N*-oxide
NOESY	nuclear Overhauser effect correlation spectroscopy
Nu	nucleophile
o	*ortho*
p	*para* (isomer)
Ph	phenyl
PHOX	phosphinooxazoline
PIFA	[bis(trifluoroacetoxy)iodo] benzene
Piv	pivaloyl
PKS	polyketide synthase
ppm	parts per million
Pr	propyl
PTC	phase-transfer catalysis
p-TsOH	*para*-toluenesulfonic acid
q	quartet (NMR spectroscopy)
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
R	undefined substituent
RCM	ring-closing metathesis
R_f	retardation factor
s	strong (IR spectroscopy)

s	singlet (NMR spectroscopy)
SAM	*S*-adenosyl methionine
SPhos	2-dicyclohexylphospino-2',6'-dimethoxybiphenyl
T	temperature
t	triplet (NMR spectroscopy)
t-	(*tert*-) tertiary (isomer)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCE	trichloroethene
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	4-methylphenylsulfonyl
vs	very strong (IR spectroscopy)
w	weak (IR spectroscopy)
WHO	world health organization
wt%	weight percent

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CHAPTER I

STUDIES TOWARD THE TOTAL SYNTHESIS OF SALIMABROMIDE

1 Introduction

1.1 Myxobacteria and their Secondary Metabolites

Myxobacteria, first discovered in 1892 by R. Thaxter,[1] belong to the δ-group of gram-negative proteobacteria and are a very rich source for secondary metabolites with diverse types of structures and fascinating biological activities. However, myxobacteria are not typical bacteria, since they are one of the bacterial groups that successfully achieved the transition from a single cell to multicellular life. They move by gliding or creeping on surfaces and are able to form complex fruit bodies. Those fruit bodies are build in times when nutrients are limited by migrating swarm colonies, which then develop macroscopic clusters and exchange extracellular chemical signals and physical contact signals (Figure 1). Within those fruit bodies, vegetative cells differentiate into myxospores. Both multicellular processes, the cooperative predation by swarm colonies and the multicellular development, are mediated by the coordinated movement of the cells and illustrate the social nature of myxobacteria. However, since they can switch between those two processes, their multicellularity is transitory and not obligatory in contrast to organisms which have no other choice than multicellularity.[2,3,4,5] Another characteristic of myxobacteria is their exceedingly large genome in contrast to other prokaryotes. The largest sequenced genome contains 14,782,125 base pairs and was isolated from the So0157-2 strain of *Sorangium cellulosum*.[6]

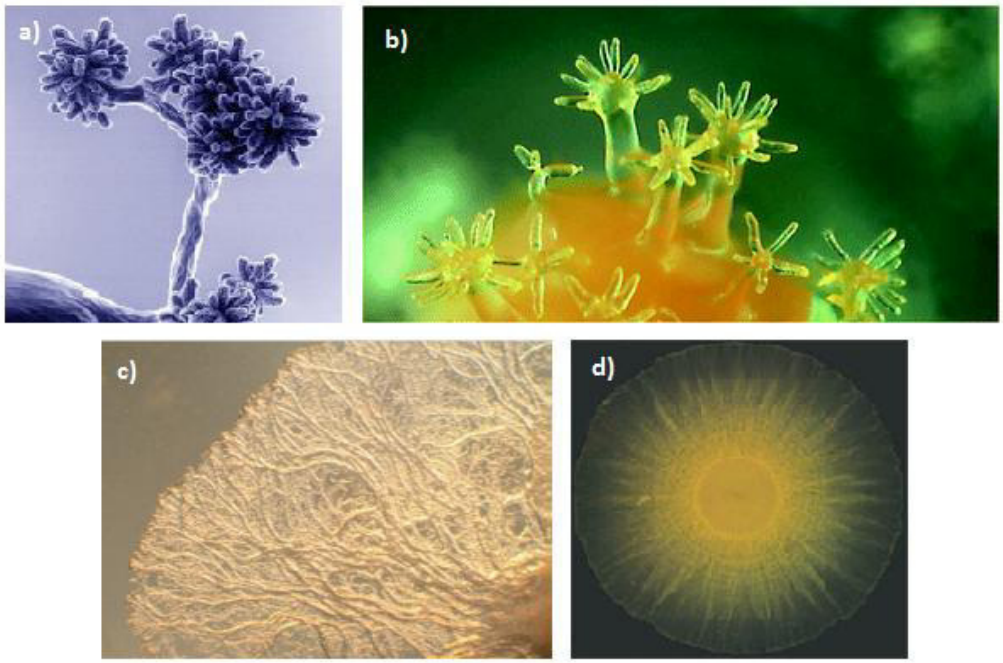
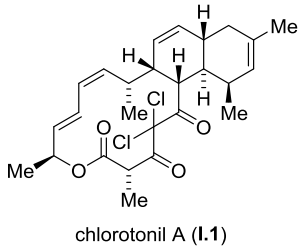


Figure 1 Fruitbodies: a)[7] and b);[8] Swarm colony: c)[3] and d).[9]

Noticeable is in particular that the metabolites of myxobacteria show modes of action, which are scarcely exhibited by other microbial natural products and are therefore very interesting as novel drug leads. Especially polyketides are often isolated of which several possess very high bioactivities, such as antiproliferative, antibiotic, antifungal and antiplasmodial activities. A representative for such a bioactive polyketide is chlorotonil A (**I.1**) (Figure 2).[2] It was isolated from the soil-dwelling myxobacterium *Sorangium cellulosum* So ce1525[4] and has already been asymmetrically synthesized by Kalesse in 2008.[10] It shows remarkable antibacterial and antimalarial activities, as it is active against all blood stages of *P. falciparum* and also against gametocytes. It proved also to be effective *in vivo* after oral administration, however, its poor solubility prevents at the moment clinical development.[4]



chlorotonil A (**I.1**)

Figure 2 Structure of chlorotonil A (**I.1**).

Another important class of myxobacteria derived polyketides is the epothilone family, produced by *Sorangium cellulosum*, strain So ce90, and isolated first in 1985 by H. Reichenbach (Figure 3). Several representatives of this class are highly bioactive, since they act as microtubule-stabilizing agents, similar to taxol.[11] Epothilon D (**I.2**) for example was identified as selective inhibitor of early steps of HIV infection (EC_{50} 0.5 nM; selectivity index SI 24.4)[4] and was also tested in clinical trials due to its potent antitumor activity (phase II, abandoned).[11] Epothilone B (**I.3**) reached phase III trials for patients with advanced ovarian cancer, but failed unfortunately in the end.[12] The most successful member of the epothilones is the semisynthetic derivative ixabepilone (**I.4**). In 2007 it granted FDA approval for "treatment of metastatic or advanced breast cancer, either as single agent or in combination with capecitabine, and will be marketed in the US by Bristol-Myers Squibb (BMS) under the trade name Ixempra®".[11]

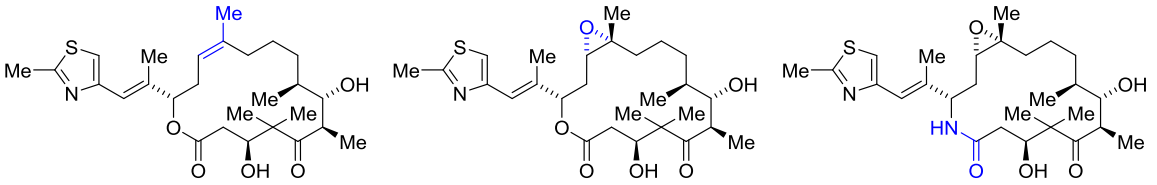


Figure 3 Structures of epothilone D (**I.2**), epothilone B (**I.3**) and ixabepilone (**I.4**).

Due to their importance as drug candidates, several total syntheses were reported by Danishefsky[13,14,15], Nicolaou[16,17,18], Schinzer[19], Sinha[20], Carreira[21] and Shibasaki[22] amongst others. Ixabepilone (**I.4**) was prepared by a semisynthetic approach from epothilone B (**I.3**) in a three step, one-pot sequence.[23]

Although it was believed for a long time that there are only terrestrial myxobacteria, marine myxobacteria were discovered in recent years and they are phylogenetically quite distinct. Since their cultivation and isolation is very difficult and often not possible at all, only a few obligate genera (*Enhygromyxa*, *Haliangium* and *Plesiocystis*) are known. They are strictly halophilic and need sea-like salinity conditions to grow. The first isolated secondary metabolite that occurs from strict marine myxobacterial origin is haliangicin (**I.5**) from *Haliangium ochraceum*, which shows antifungal bioactivity against *Aspergillus niger* (AJ117374, MIC: 12.5 µg mL^{-1}) and *Fusarium* sp. (AJ177167, MIC: 6.3 µg mL^{-1}) (Figure 4). Interestingly, the production of haliangicin (**I.5**) is dependent of the NaCl-concentration and is optimal at 2–3% NaCl (w/v). This is also the best concentration for optimal growth.[24,25]

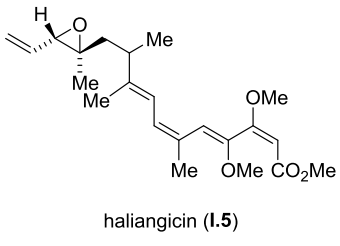
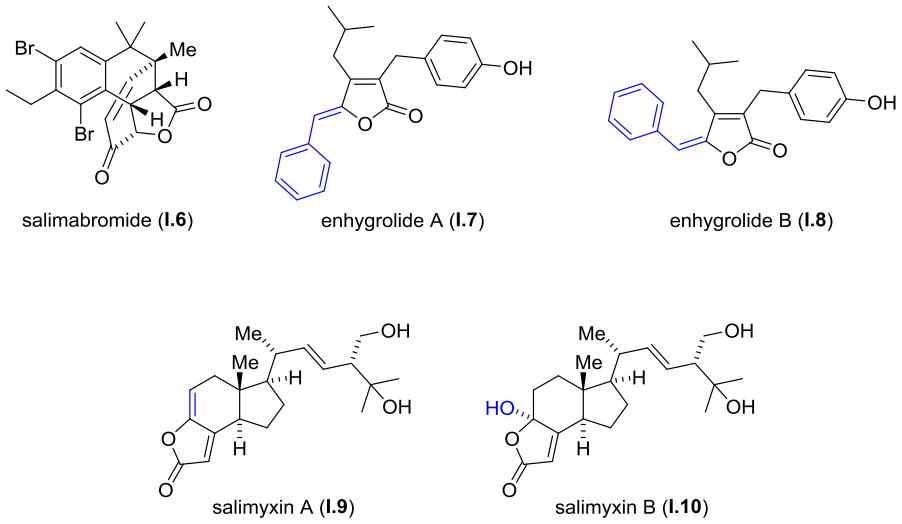


Figure 4 Structure of haliangicin (**I.5**).

Another obligate marine myxobacterium is the genus *Enhygromyxa*. This species is truly halophilic and was isolated from coasts from all over the world. A NaCl-concentration of 1–2% at a pH range of 7.0–8.5 seems to be optimal for growth. Five structures of presumably

polyketide, shikimate and terpenoid origin have been isolated and described: the polyketide salimabromide (**I.6**), the enhygrolides A (**I.7**) and B (**I.8**), formed by the shikimic acid pathway, and the terpenoids salimyxins A (**I.9**) and B (**I.10**) (Figure 5). The structure of the enhygrolides resembles the ones of cyanobacteria-derived metabolites. Both were tested for their biological activity, but only enhygrolide A (**I.7**) showed some activity against *Arthrobacter cristallopoietes* with an MIC value of 4 μg mL^{-1}. The salimyxins belong to the terpenoid subgroup of incisterols and are presumably degraded sterols. Similar to enhygrolide A (**I.7**), the salimyxins show only biological activity against *Arthrobacter cristallopoietes* with an MIC value of 8 μg mL^{-1} and 4 μg mL^{-1}, respectively.[4,24]



salimabromide (**I.6**) enhygrolide A (**I.7**) enhygrolide B (**I.8**)

salimyxin A (**I.9**) salimyxin B (**I.10**)

Figure 5 Structures of salimabromide (**I.6**), enhygrolides A (**I.7**) and B (**I.8**) and salimyxins A (**I.9**) and B (**I.10**).

1.2 Halogenated Natural Products of Marine Origin

The use and isolation of biologically occurring substances is known for a very long time, but the main focus was on terrestrial natural products, due to their easier accessibility. However, since the beginning of the 1970s the average number of isolated and characterized marine natural products increased steadily and in the year 2007 over 1000 new compounds were described.[26] This effect can be attributed amongst other things to new isolation and cultivation techniques, like marine bioprocessing, and remote submersibles, which are able to access new depth in the oceans. Data from 2001–2007 show particularly increasing average numbers of isolated new compounds from the Caribbean, the China Sea, the Indian Ocean, Japan and the Western Pacific (Figure 6b). Also noticeable is the spectacular increase of natural products isolated from microorganisms (Figure 6a). Comparison of the data of 2007 with the average of 1965–2005

reveals a rise by 600%. This reflects the augmented interest in bacteria and fungi from marine origin. The numbers for the more traditional categories such as sponges and cnidarians remain steadily very high.[27,26]

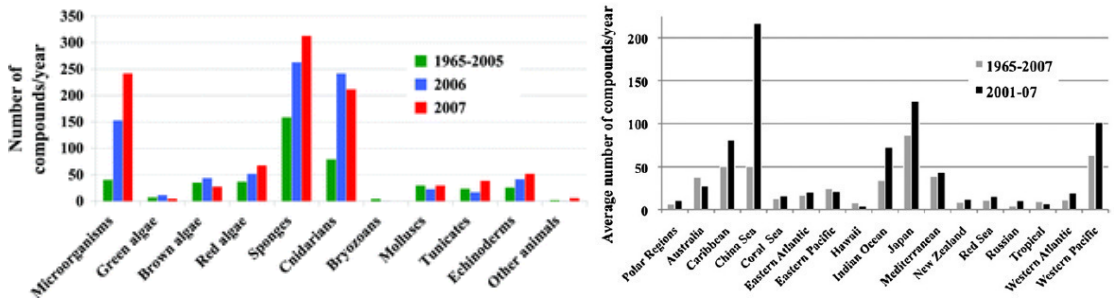


Figure 6 a) Distribution of marine natural products by phylum.[26] b) Trends in geographic distribution of collection sources.[26]

An estimated number of over 15000 marine natural products of all types have been described in total and around 15–20% of them (survey of the literature from 1998–2005) are organohalogens.[28] This is quite surprising, since in 1961 no halogenated substances from marine origin were known, except for iodinated tyrosine derivatives, and even in 1973, only 50 of them had been discovered.[29] Since then, a huge number of marine organohalogens was observed. Due to the high halide concentrations in the oceans in contrast to the terrestrial occurrence (Table 1), it is not astonishing that most of the halogenated natural products arise from marine organisms. They were isolated from a huge number of organisms, such as sponges, cyanobacteria, molluscs, sea hares, mussels, bryozoans (moss animals), tunicates, soft corals, symbiotic bacteria, marine phytoplankton, macroalgae, marine bacteria and marine fungi.[28]

Table 1 Distribution of halides/mg kg^{-1} in the environment.[28]

Halide	Oceans	Sedementary rocks	Fungi	Wood pulp	Plants
Cl^-	19000	10–320		70–2100	200–10000
Br^-	65	1.6–3	100		
I^-	0.05	0.3			
F^-	1.4	270–740			

1.2.1 Selected Halogenated Marine Natural Products

In particular the chloride concentration is extremely high in oceans, which leads to a vast number of volatile chlorinated simple alkanes and alkenes. One of them is chloromethane (CH_3Cl) and interesting is that its natural production, mainly by salt marsh, dwarf the anthropogenic contribution. It is also the most frequent occurring organohalogen in the atmosphere. Chloroform ($CHCl_3$) is another representative, which is produced, amongst others, by green, red and brown seaweeds as well as macro- and microalgae. Studies revealed an increase in the $CHCl_3$ production through an increase in light intensity, presumably when photosynthesis reached its maximum. Similar to CH_3Cl, over 90% of the atmospheric $CHCl_3$ is derived from nature.[28] Also trichloroethene (TCE), a former dry-cleaning solvent, is produced by over 27 species of marine algae and the amounts of its emission from the oceans into the atmosphere is quite high.[30]

Although the availability of bromide is a lot lower than that of chloride, there are multiple bromine containing organohalogens, which is a result of the lower reduction potential: $E°$ = 2.87 V (F^-), 1.36 V (Cl^-), 1.09 V (Br^-), 0.54 V (I^-).[31] Bormoform ($CHBr_3$) is the major contributor of organic bromine in the atmosphere and is invariably produced by macro- and microalgae. Around 70% of the worldwide produced $CHBr_3$ stem from macroalgae. Similar to $CHBr_3$, iodomethane (CH_3I) is produced by marine algae and is often detected in the oceanic atmosphere.[28]

In general, sea-salt spray is the major source for volatile reactive organohalogens (Cl_2, Br_2, BrCl, HOCl, HOBr) in the atmosphere. These reactive species are subsequently converted to chlorine oxide and bromine oxide, which affect the ozone layer and are probably the reason for the detected low ozone concentrations over the Dead Sea and the Great Salt Lake.[28,32] However, not only halomethanes are generated by marine organisms, but a wide variety of metabolites such as polyketides, terpenoids, alkaloids, peptides, indols, fatty acids and phenols.[33] They are often of special interest for the pharmaceutical industry due to their high biological activities, which include anti-inflammatory, antibacterial, antituberculosis, antifungal, anticancer, anti-infective, antioxidant and antimicrobial activities.[34,35]

The sesterterpenoids (C_{25}) neomangicol A (**I.11**) and B (**I.12**), for example, were isolated from a marine fungus of the genus *Fusarium* and are probably the first halogenated representatives for this class of terpenoids (Figure 7). Both possess an unusual carbon skeleton that is proposed to be formed by an atypical terpenoid pathway ("head to tail" isoprene configurations). The halogenation pattern is also of interest, since it constitutes of a vinyl dihalogen group.

Negmangicol A (**I.11**) appeared to be active against MCF-7 (human breast carcinoma) and CACO-2 (human colon carcinoma) cell lines (IC_{50} = 4.9 and 5.7 μM, respectively). **I.12** however, showed antibacterial activity against the Gram-positive bacterium *Bacillus subtilus*, similar to the activity of the antibiotic gentamycin. The halogenation pattern seems to influence the biological activity, since their nonhalogenated analog neomangicol C (**I.13**) does not show any effect at all.[36] Until today no total synthesis of any neomangicol was reported, but only a synthesis of the tetracyclic core of neomangicol C (**I.13**) by Sarpong.[37]

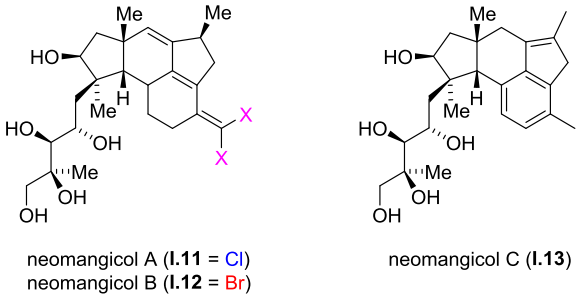


Figure 7 Structures of neomangicol A (**I.11**), B (**I.12**) and C (**I.13**).

Fluorinated natural products are in general very rare, due to the difficult accessibility of fluoride arising from its physical and chemical properties, but marine fluorinated organohaloges are especially scarce. In 2003, the first natural organofluorines from a marine source were described, which were isolated from the marine sponge *Phakellia fusca*. The group of Xiao-Hua Xu reported five 5-fluorouracil compounds, which are shown in Figure 8. The structures of **I.14**, **I.15** and **I.18** were new, but the ones of fluorouracil (**I.16**) and **I.17** were known previously.[38] Fluorouracil (**I.16**) was synthetically obtained in 1957[39] and is a prevalent antitumor agent against a variety of cancer types and also part of the WHO model list of essential medicines.[40]

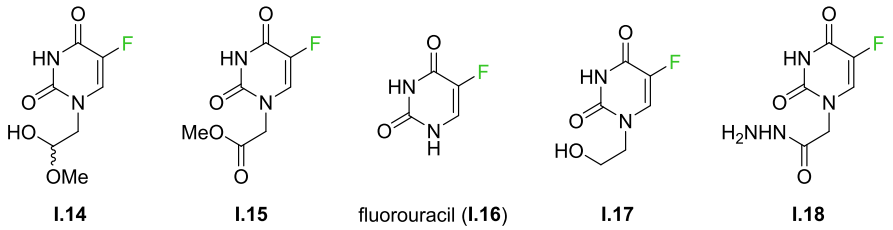
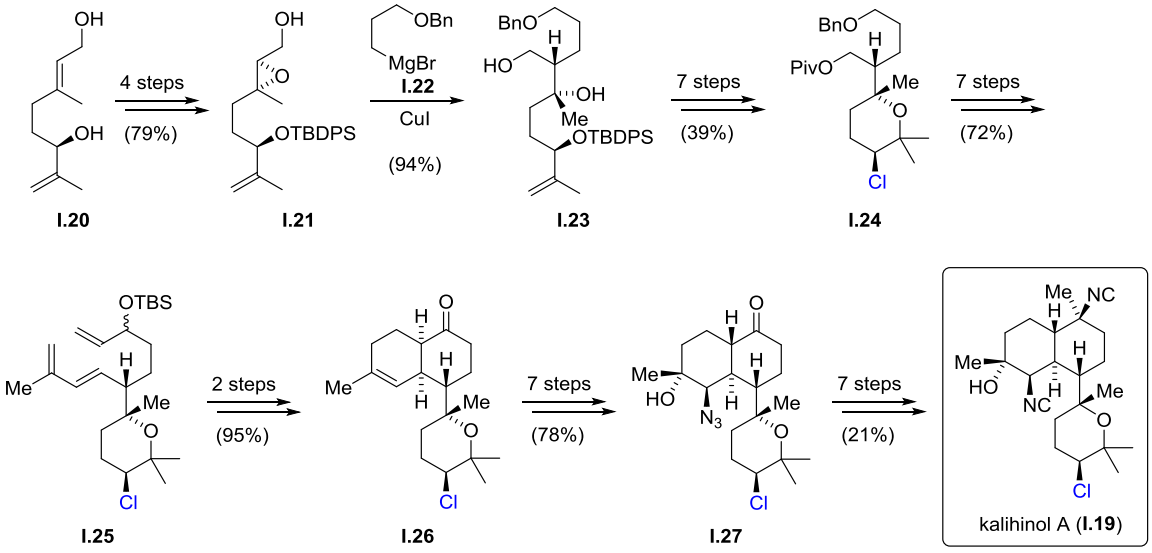


Figure 8 Structures of fluorouracil (**I.16**) and derivatives thereof.

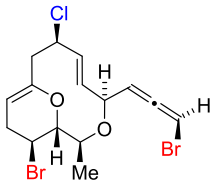
Kalihinol A (**I.19**), a chlorinated representative of the huge family of highly functionalized kalihinane diterpenoids, was isolated from the sponge *Acanthella* in 1984 (Scheme 1).[41] Several members of this family possess biological activities such as antifungal, antifouling, antimicrobial, cytotoxic and anthelminic properties. However, kalihinol A (**I.19**) is up to now the most potent of all tested isocyanoterpenes. **I.19** turned out to be remarkably active against the malaria transmitting parasite *Plasmodium falsiparum* (EC_{50} = 1.2 nM) and shows also an exceptional selectivity index (SI = 317), which was defined as the ratio of FM3A cell cytotoxicity to *Plasmodium falsiparum*.[42,43,44] A total synthesis with 35 steps was achieved by Miyaoka. At the beginning, epoxide **I.21** is synthesized in four steps, including a Sharpless asymmetric epoxidation. Diol **I.23** was afforded by nucleophilic alkylation with Grignard reagent **I.22** and additional seven steps were required to form the chlorinate tetrahydropyran ring of **I.24**. Triene **I.25** for the intramolecular Diels-Alder reaction, to form the decalin system, was achieved in seven steps. Deprotection of the TBS-group and oxidation resulted in the ketone, which spontaneously underwent the Diels-Alder reaction to generate selectively *cis*-decalin **I.26**. This was then transferred into *trans*-decalin **I.27** in seven steps, introducing also an azide moiety. In the last seven steps, the azide was transformed into an isocyanide and the ketone into a methyl and isocanide group.[44]



Scheme 1 Structure and total synthesis of kalihinol A (**I.19**).

A very interesting structure is the one of obtusallene I (**I.28**), isolated from the red alga *Laurencia obtuse* in 1982, which was not only determined by NMR spectroscopy, but also verified by X-ray analysis.[45] Obtusallene I (**I.28**) belongs to a large family of halogenated C_{15}-acetogenins and

possesses the typical bromide substituent in β-position to the acetogenic oxygen (Figure 9). Another typical feature is the bromoallene unit. To date, no total synthesis of **I.28** or a structurally related member of this family was reported. However, Braddock published a possible biosynthesis starting from a linear precursor, involving several electrophilic bromination events.[46,34]

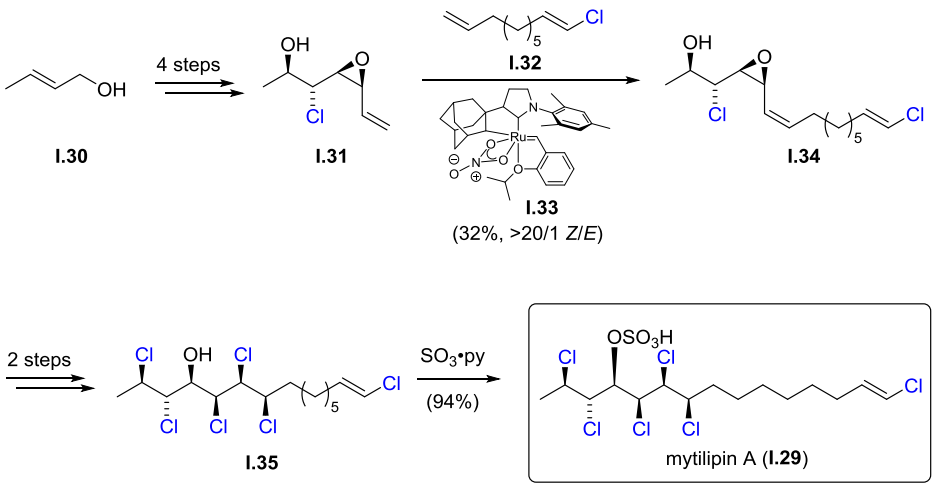


obtusallene I (**I.28**)

Figure 9 Structure of obtusallene I (**I.28**).

Chlorosulfolipids are known for a long time since they are, together with other toxins, responsible for seafood poisoning in humans. However, the mechanism of their biological activity is still unknown. They were first isolated from freshwater microalgae (e. g. *Ochromonas danica* and *Ochromonas malhamensis*) of which they constitute 15% of all lipids. The cytotoxin mytilipin A (**I.29**) is a relatively small representative of the chlorosulfolipids compared to other members of this family (Scheme 2). **I.29** was isolated in 2001 from 4.3 kg of digestive glands of mussels from the genus *Mytilus galloprovincialis*, collected along the coast of the Emilia Romagna. However, it is not sure if the mussels produce **I.29** by themselves, or accumulate harmful microalgae. Tests to reveal the bioactivity of mytilipin A (**I.29**) showed antiproliferative activity on the J774 (murine monocyte/macrophage), WEHI 164 (murine fibrosarcoma), and P388 (murine leukemia) cell line as well as inhibition of growth in all investigated cell lines, evaluated after 72 h (IC_{50} of 12.1, 16.3, and 10.4 μg/mL, respectively).[47,48,49] Due to its unique structure, the polyhalogenated backbone, **I.29** is a challenging target for total synthesis. The first synthesis of racemic **I.29** was published by Carreira in 2009,[49] followed by an enantioselective synthesis by Yoshimitsu[50] and a very concise synthesis (7 or 8 steps, respectively) by Vanderwal.[51] The latter is depicted in Scheme 2 and commences with a four step synthesis of racemic vinyl epoxide **I.31** from commercially available crotyl alcohol (**I.30**). At this stage, the epoxide could undergo a kinetic resolution to afford enantioenriched material for an enantioselective synthesis. *Z*-selective alkene cross-metathesis using Grubbs cycloadamantyl catalyst **I.33** gave vinyl epoxide **I.34** in only 32% yield but excellent selectivity. Two further steps provided

hexachlorinated alcohol **I.35**, which was treated under conditions reported by Carreira to complete the synthesis of **I.29**.[51]

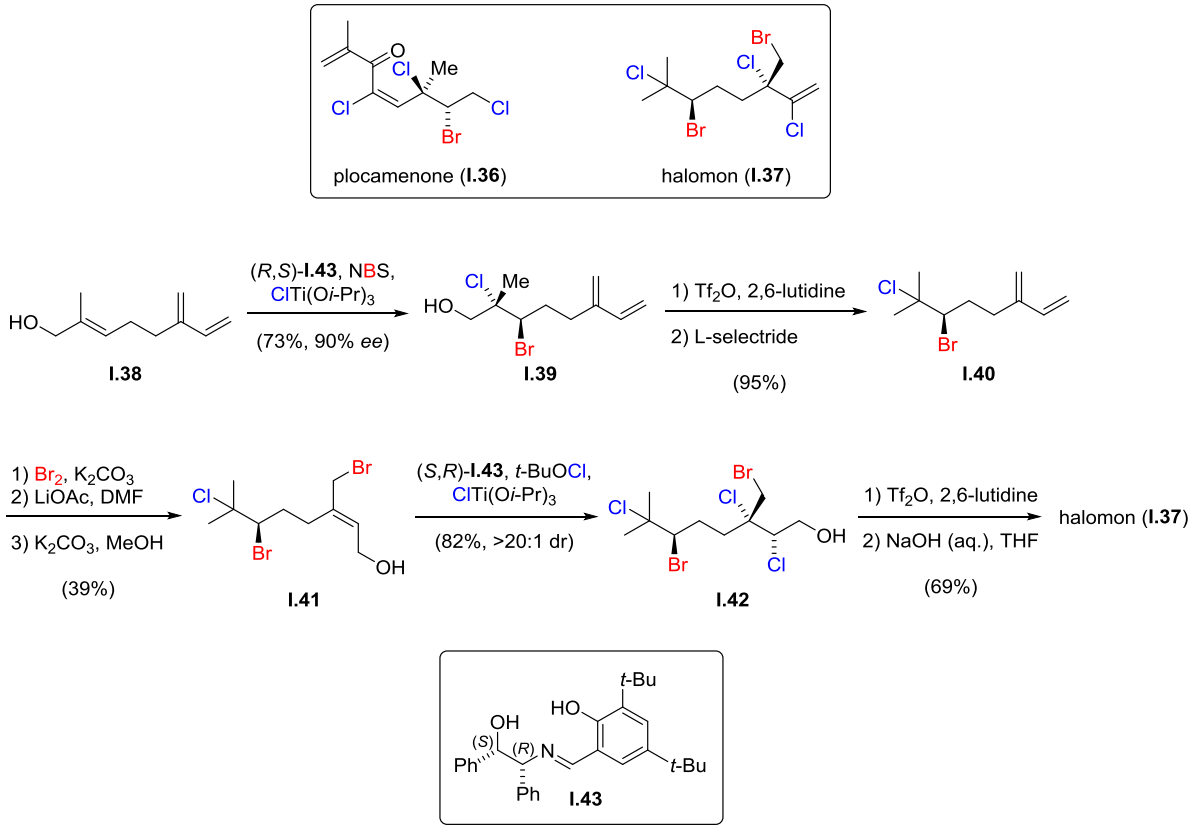


Scheme 2 Structure and total synthesis by Vanderwal of mytilipin A (**I.29**).

The class of vicinal bromochlorinated natural products contains over 160 substances, whereby many of them are highly bioactive.[52] One of them is the tetrahalogenated terpene plocamenone (**I.36**), isolated from the red alga *Plocamium angustum* (Scheme 3). Its structure was revised several times, until it was unequivocally identified as the one depicted.[53] The difficulty to elucidate the correct molecular structure concerns the whole family of polyhalogenated monoterpenes. NMR studies of the noncrystalline terpenes to clarify their structures are challenging as described by several studies.[54] Moreover, they are often relatively volatile and tend to decompose or isomerize, as in the case of isoplocamenone, which isomerizes to plocamenone (**I.36**) upon exposure to light.[52]

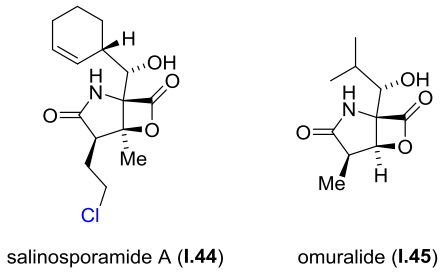
The most exciting one of the vicinal bromochlorinated natural products is halomon (**I.37**), which was first isolated in 1975 from the red alga *Chondrococcus hornemannii* and fully described and analyzed in 1992 (Scheme 3). The structure elucidation appeared to be very difficult, as reported for plocamenone (**I.36**), but X-ray crystallography and extensive NMR studies confirmed the proposed structure. In first biological tests **I.37** appeared to be inactive in the anti-HIV assay, but highly cytotoxic against human cancer cells. Extended screenings at the NCI (National Cancer Institute) revealed that **I.37** was "one of the most extreme examples of differential cytotoxicity".[55] Most sensitive to halomon (**I.37**) treatment were brain tumor, renal and colon tumor cell lines, compared to the less sensitive melanoma and leukemia cell lines. As a

result of this extraordinary activity, the NCI decided to use **I.37** in preclinical drug development. Although the first results were encouraging, these studies were unfortunately abandoned, since it was not possible to gain enough material of **I.37**. All efforts to isolate enough material from natural sources were unsuccessful, probably as a result of seasonal and local deviation of the terpene concentration in the algae.[55,56,52] Since the natural sources cannot provide sufficient amounts of the drug, total synthesis could be a solution to this problem. The first selective synthesis of (+)-**I.37** was reported by Burns in 2009, who was able to synthesize the target molecule in nine steps and 400 mg of **I.37** in total. The synthesis starts with the enantioselective bromochlorination of allylic alcohol **I.38** with the (*R*,*S*)-Schiff base **I.43**. Deoxygenation afforded the bromochlorinated myrcene derivative **I.40**, which was subjected to formal 1,4-bromohydration conditions. Bromohydrin **I.41** was dichlorinated with the (*S*,*R*)-Schiff base **I.43** with excellent results. The final product **I.37** was obtained in two further steps in good overall yield.[52]



Scheme 3 Structures of plocamenone (**I.36**) and halomon (**I.37**) and total synthesis of **I.37**.

One of the most interesting organohalogen is currently salinosporamide A (Marizomib, NPI-0052) (**I.44**), isolated from the obligate marine actinomycete *Salinispora tropica* (Figure 10). It is a high functionalized γ-lactam-β-lactone with outstanding biological activity. **I.44** is an irreversible proteasome inhibitor (IC_{50} value of 1.3 nM) and thus approximately 35 times more effective than omuralide (**I.45**) (IC_{50} value of 49 nM). Furthermore, **I.44** displays high in vitro cytotoxicity against several tumor cell lines (IC_{50} values of 10 nM or less). At the moment it is tested in phase I clinical trials against advanced malignancies including multiple myeloma.[57]

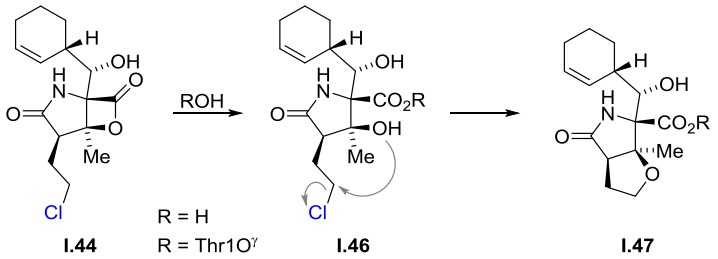


salinosporamide A (**I.44**) omuralide (**I.45**)

Figure 10 Structures of salinosporamide A (**I.44**) and omuralide (**I.45**).

Salinosporamide A (**I.44**) is also a good example to show the influence of the halogen substituent on the biological activity. Tests with different substitution patterns, replacing the chlorinated ethyl group by simple alkyl groups showed a dramatic decrease in activity. In contrast, substitution of the chloride by bromide or iodide did not affect the potency. These findings lead to a proposed mechanistic role of the chlorinated ethyl group. The β-lactone is opened by the nucleophilic addition of the hydroxyl group of Thr1O^{γ}, followed by intramolecular S_N2-displacement to generate the tetrahydrofuran ring (**I.46→I.47**) (Scheme 4). This reaction sequence results in an irreversible covalent inhibition of the proteasome, a key player of the protein degradation pathway, and underlies the elegant way of action of this inhibitor.[58]

Since this organohalogen **I.44** was identified as potential drug lead, several groups of organic chemists tried to investigate a total synthesis. In 2004, Corey[59] was the first to report an enantiospecific synthesis, followed by Danishefsky[60] in 2005 and several others in the past few years.[61]

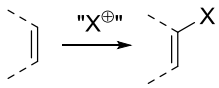
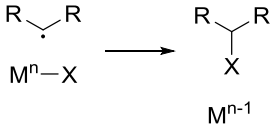
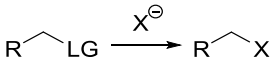


Scheme 4 Simplified mechanism of hydrolysis and subsequent rearrangement of **I.44** in aqueous solution (R = H) or in the binding pocket of proteasome core particle (R = Thr1Oγ).

1.2.2 Biosynthesis of Halogenated Natural Products

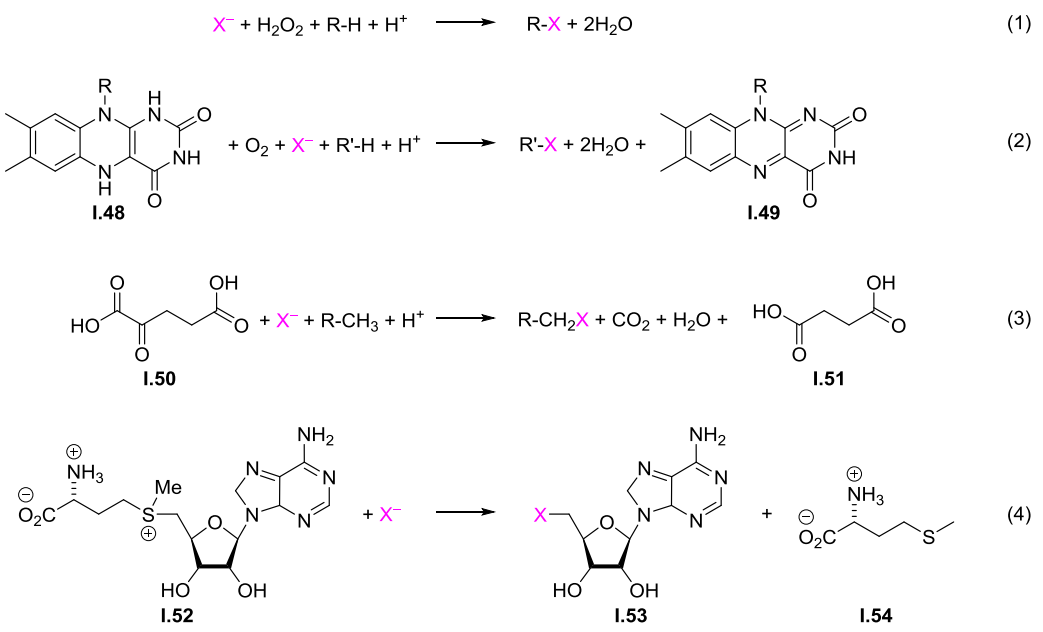
As shown before, incorporation of halogen atoms profoundly influences the biological activity of secondary metabolites. Thus, the exploration of the biosynthesis of those organohalogens is an important research field. In general, there are three different types of halogenases that are able to catalyze halogenation reactions. The classification was carried out according to the chemical nature of active halogen species (Table 2). The primary halogen sources for all halogenases are solvated halide anions.[62]

Table 2 Biohalogenation pathways.

Electrophilic	**Radical**	**Nucleophilic**
		
XO^-	$X^\bullet$	X^-
Haem-dependent haloperoxidases	Non-haem iron/2-oxoglutarate dependent halogenases	SAM fluorinase
Vanadate-dependent haloperoxidases		SAM chlorinase
Flavin-dependent halogenases		SAM-dependent halide methyl transferase

The first type catalyzes electrophilic halogenations by oxidation of a halide anion to an electrophilic halonium species "X^+". This gets then transferred to a nucleophilic system, such as an alkene or an aromatic compound. The three halogenases use different ways to oxidize X^- to hypohalous acid HOX or hypo halite XO^-, respectively. While the haem- and vanadium-dependent haloperoxidases (HPO) require H_2O_2 in combination with a metal co-factor, the flavin-dependent halogenases use O_2 in the form of a hydroperoxyflavin (FADHOOH) intermediate. This is activated by the flavin co-factor FAD (flavin adenine dinucleotide).[62] The overall stoichiometry of halogenations via haloperoxidases and flavin-dependent halogenases is depicted in Scheme 5, equation 1 and 2.[63]

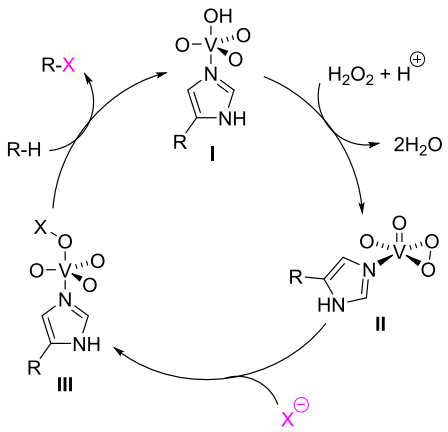
A well-known member of the haloperoxidases is the chloroperoxidase (CPO), first isolated as haem-dependent CPO in 1966 from the terrestrial fungus *Caldariomyces fumago*.[64] An important fact is that the CPO cannot only oxidize Cl^-, but also Br^- and I^- to HOX. In contrast, the bromoperoxidase (BPO) utilizes just Br^- and I^-.[63]



Scheme 5 Overview over the different types of halogenation reactions: (1) electrophilic halogenation via haloperoxidases; (2) electrophilic halogenation via flavin-dependent halogenases; (3) radical halogenation via 2-oxoglutarate (**I.50**) dependent non-haem iron halogenases; (4) nucleophilic halogenation via SAM-dependent halogenases.

For halogenations in marine environment, especially the vanadium-dependent haloperoxidases (V-HPO) are thought to be responsible. A vanadate ion is thereby ligated to a histidine residue

of a protein to keep the co-factor trapped in the active site of the enzyme. A proposed catalytic cycle for the reaction is depicted in Scheme 6. The resting state of vanadium complex **I** gets activated by H_2O_2 to generate V(V) peroxide complex **II**. This complex is then able to oxidize a halide ion to a vanadium bound hypohalous acid **III**. Probably, this active halogenation species stays at least in close proximity to the enzyme, since V-HPOs have shown to be more selective than Fe-HPOs. In contrast to the heme-dependent HPOs, the oxidation state of the metal center stays constant.[28,62,63,65] However it has to be noted, that the depicted catalytic cycle is speculative, for which reason the protonated state of the complexes is not shown.



Scheme 6 Proposed catalytic cycle of a vanadium-dependent haloperoxidases (V-HPO).

The halogenation of inactivated carbon centers proceeds by a radical rebound mechanism. Thereby, an Fe(IV) oxido species is generated via binding of O_2 to the Fe(II) center followed by oxidative decarboxylation of α-ketoglutarate to succinate (Scheme 5, equation 3).[62,63,65]

Organofluorine compounds are very rare in nature. This observation can be explained by the fact that neither H_2O_2 nor O_2 are able to oxidize F^- to either $F^{\bullet}$ or F^+, as a reason of the high reduction potential of fluorine.[63] Thus, the halogenases, working best for chlorine, bromine and iodine are not able to catalyze fluorinations. The only possibility is to use the nucleophilic F^- directly as the halogenating agent, but the naked F^- is very difficult to generate in aqueous media. The only reported enzyme to catalyze a fluorination is FlA (5'-fluoro-5'-deoxyadenosinesynthase) and also accepts Cl^-. SAM (*S*-adenosyl-L-methionine, **I.52**) is not a co-factor in these reactions, but functions as a substrate, unlike to the SAM-dependent halide methyl transferases. The formation of the C-F bond proceeds via an S_N2-type reaction of F^- to SAM (**I.52**), which contains the very good leaving group methionine (Figure 11).[62,65] A similar

transformation is also known for the SAM chlorinase SalL and the product of both halogenation reactions is the corresponding halogenated adenosine derivative. 5'-chloro-5'-deoxyadenosine is physiologically used to generate chloroethylmalonyl-CoA, which is then incorporated into salinosporamide A (**I.44**).[63] The large amounts of halogenated methanes CH_3X (X = Cl, Br, I) are produced by SAM-dependent halide methyl transferases, via a nucleophilic attack at the methyl group instead of the adenosine part (Figure 11).[62]

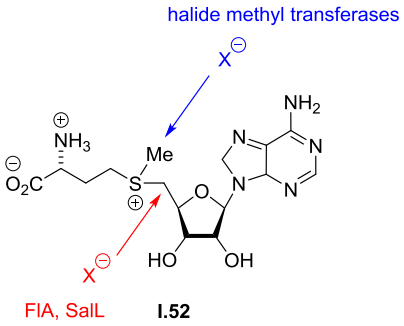
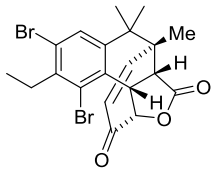


Figure 11 Halogenase catalyzed nucleophilic attack on SAM.

2 Results and Discussion

In 2013, G. König and co-workers reported on the isolation of the unique structure of the natural product salimabromide (**I.6**) (Figure 12) from a mud sample from the coast of the German island Prerow. It turned out to be a novel secondary metabolite of the genome strain SWB007 of the obligatory marine myxobacterium *Enhygromyxa salina*. Due to the fact that only minor amounts of the natural product are produced (8 μg L^{-1}) and out of 64 L culture just 0.5 mg of **I.6** could be isolated, only a few tests of its biological activity were performed. However, an inhibitory activity against *Arthrobacter crystallopoietes* (MIC value of 16 μg mL^{-1}) was observed.[25,24]

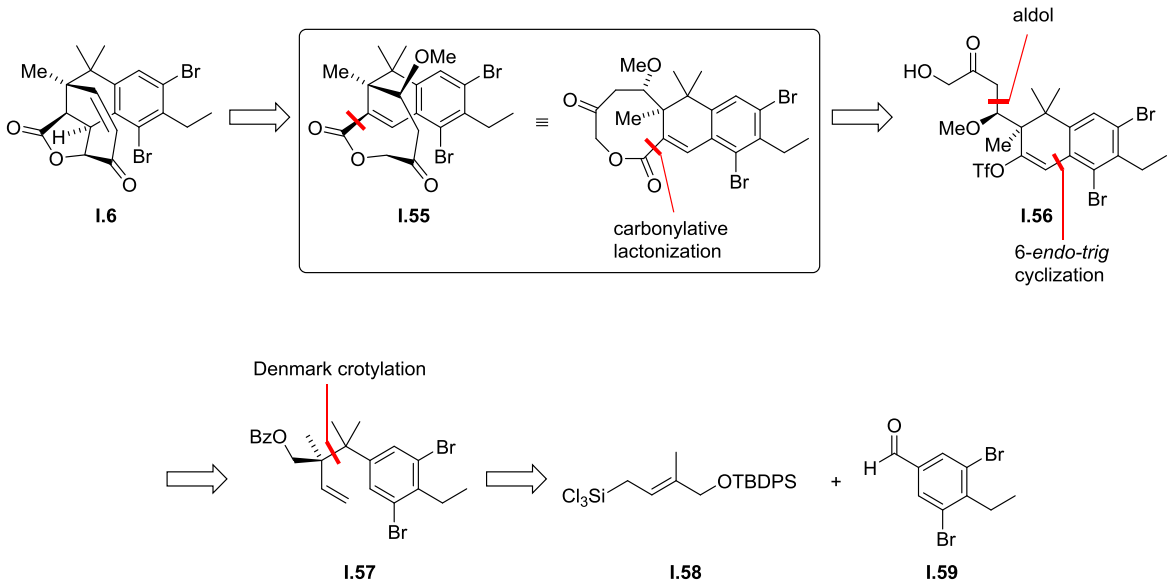


salimabromide (**I.6**)

Figure 12 Structure of salimabromide (**I.6**).

The authors of the isolation paper also suggest that the biosynthesis of salimabromide (**I.6**) is in principle carried out by a polyketide synthase (PKS) III cluster adjacent to at least one halogenase. Halogenated metabolites from marine myxobacteria are in general very rare and the same holds for pure PKS-derived compounds, which makes the structure of the new natural product even more interesting. **I.6** consists of an unrivaled tetracyclic core structure, containing a dibrominated tetraline subunit and a γ-butyrolactone moiety, which are bridged by a cycloheptenone. Moreover, the structure consists of four consecutive stereogenic centers of which one is an all carbon quaternary center. Adjacent to this, another all carbon quaternary center is positioned. The ethyl side-chain of the benzene ring is rarely found in natural products. The structure determination was carried out by extensive NMR analysis and via comparison of the experimental and the calculated circular-dichroism (CD) spectroscopic data.[1,2] The predicted structure was validated in 2017 by Kutateladze, who published studies on "parametric corrections to DFT-computed ^{13}C NMR chemical shifts and spin−spin coupling constants"[66] which allow a fast comparison of measured and predicted NMR data.

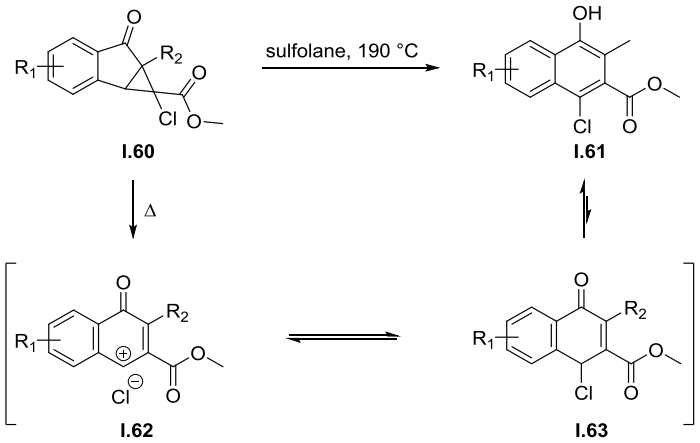
Due to its fascinating new structure and its low natural abundance salimabromide (**I.6**) represents an attractive target for total synthesis. So far, only one toward synthesis was published. Menche and Schmalzbauer reported in 2015 the synthesis of the tricyclic core **I.55** of salimabromide (**I.6**) in 22 steps (longest linear sequence). Their idea was to synthesize an eight membered lactone ring, which should be used to build the γ-lactone and the cycloheptenone subsequently (Scheme 7). To generate the eight membered lactone ring **I.55**, they applied a site-selective carbonylative lactonization, which surprisingly did not affect the bromine substituents, but proceeded in only 31% yield. The side-chain of **I.56** was introduced by an aldol reaction and the tetraline core was closed by an *endo*-selective iodocyclization. The chiral quaternary center of **I.57** was set by an asymmetric Denmark crotylation in 85% yield and 95% *ee*. The two precursors **I.58** and **I.59** for the synthesis were prepared in five and four steps, respectively.[67]



Scheme 7 Retrosynthetic analysis of salimabromide (**I.6**) by Menche and Schmalzbauer.

2.1 First Generation Approach

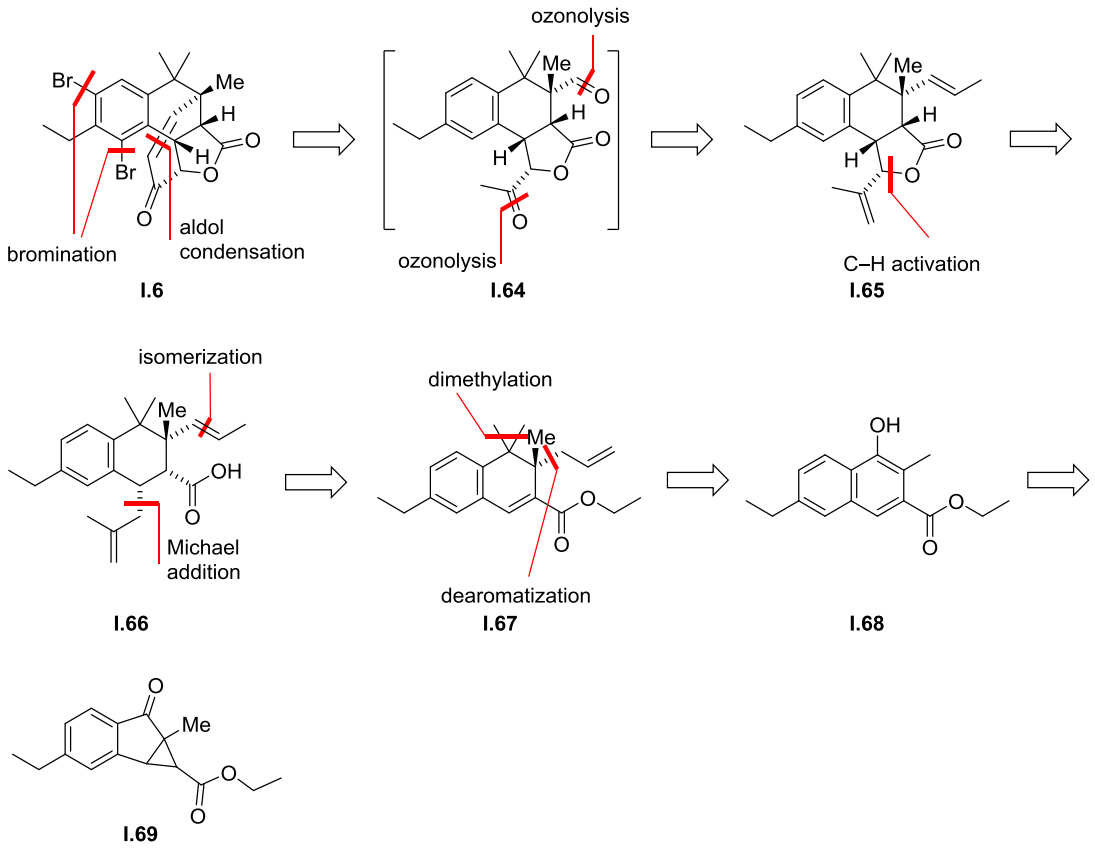
The aim of this thesis was the development of a total synthesis of salimabromide (**I.6**) to provide some material for detailed biological testings. The retrosynthetic planning hinged on the idea to build up the tetraline core by our previously developed fragmentation methodology. This provides highly substituted 1-naphthols **I.61**, which can be further functionalized (Scheme 8).[68]



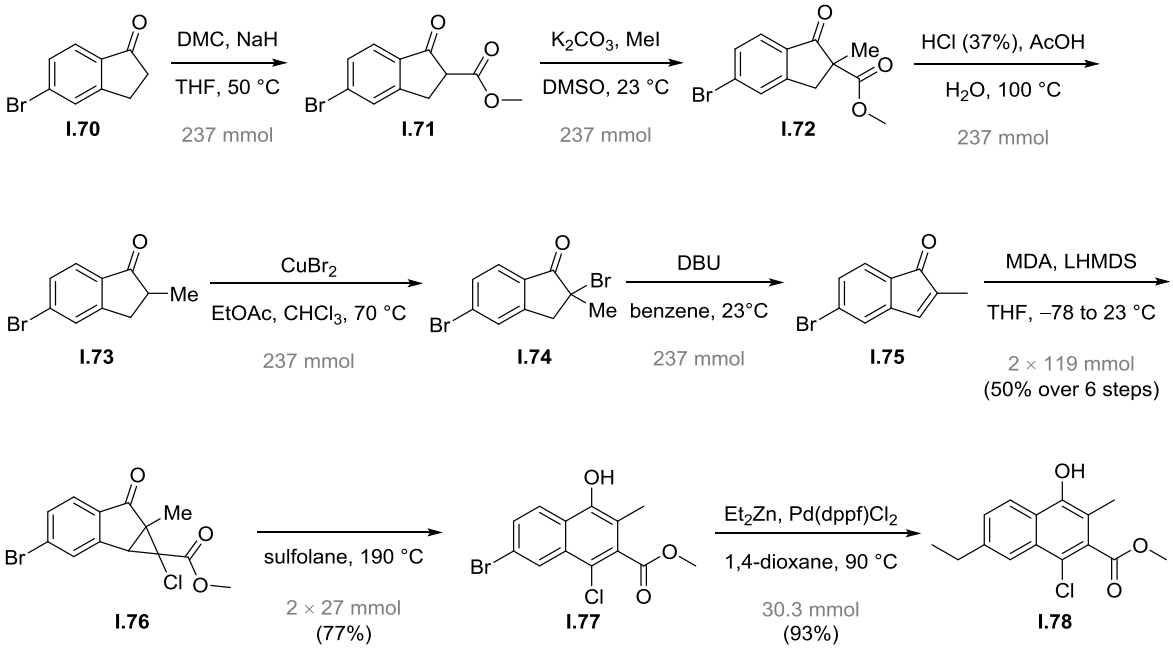
Scheme 8 Electrocyclic ring-opening and 1,2-chloride migration.

The detailed retrosynthesis of **I.6** is depicted in Scheme 9 and started with a double bromination of the aromatic ring, followed by an aldol condensation of the ozonolysis product **I.64** (Scheme 9). The furano lactone **I.65** was envisaged to be formed by an allylic C–H activation using the methodology developed by C. White.[69,70] The double bond of the allyl group at the quaternary center should be isomerized[71] and the second allylic side chain should be introduced via a Michael addition. Precursor **I.67** is envisioned to be formed by a dearomatization reaction[72] of the corresponding naphthol **I.68**. This would generate a tetralone derivative, which could be transformed into the second quaternary center by a *gem*-dimethylation. Naphthol **I.68** was expected to be accessible by the fragmentation of **I.69**.[68]

Starting from 5-bromo-1-indanone (**I.70**), the first steps were the formation of β-keto ester **I.71**,[73] followed by an alkylation[74] and a Krapcho decarboxylation[75] under strongly acidic conditions (Scheme 10). Subsequent bromination with $CuBr_2$[76] and elimination with DBU[77] afforded indenone **I.75**, which was cyclopropanated with methyl dichloroacetate (MDA).[78] At this stage, the first purification by column chromatography was required to afford the cyclopropanated indenone **I.76** in 50% yield over six steps. The ensuing fragmentation reaction (sulfolane, 190 °C) afforded naphthol **I.77** in very good yield.[68] The palladium-catalyzed Negishi cross-coupling of **I.77** with diethyl zinc was performed on a 30.3 mmol scale and gave naphthol **I.78** in excellent yield.[79]

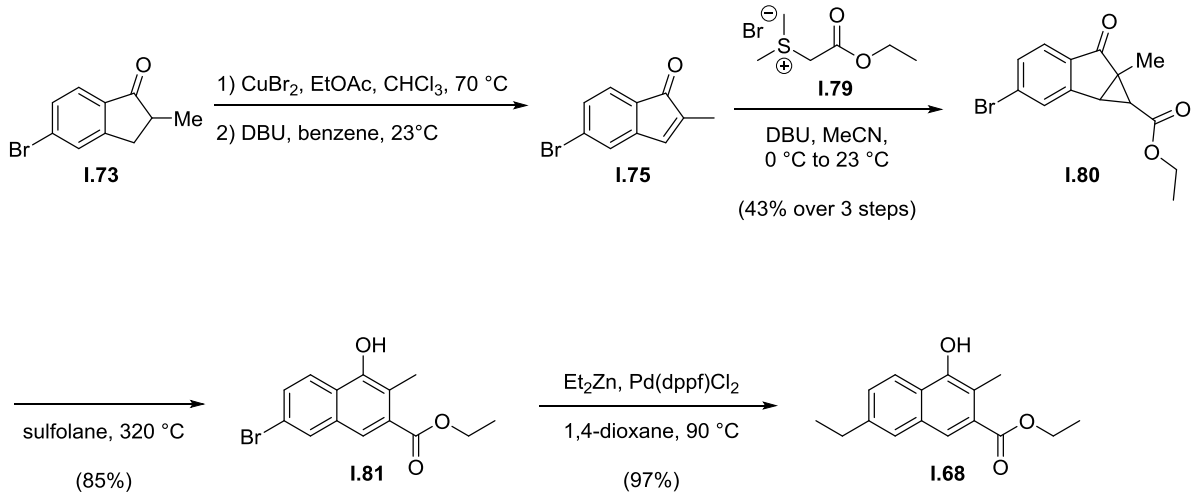


Scheme 9 Retrosynthesis of salimabromide (**I.6**).



Scheme 10 Synthesis of chlorinated naphthol **I.78**.

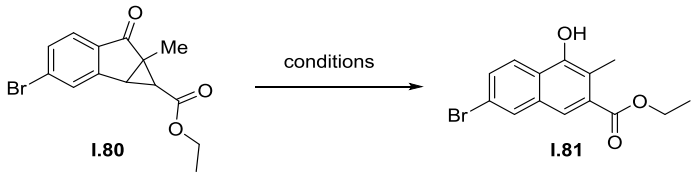
In parallel, we investigated the synthesis of the non-halogenated naphthol **I.68** (Scheme 11). The beginning of the synthesis was the same as outlined for the halogenated naphthol **I.78**, but the reagent for the cyclopropanation was dimethylsulfonium bromide **I.79** this time.[80] With this, the cyclopropanated product **I.80** was obtained in 43% yield over three steps. The fragmentation of this substrate turned out to be challenging, since no reaction was observed at 190 °C (Table 3, entry 1). The use of neat **I.80** or the addition of allyl acohol or allyl amine had no effect on the reaction and only starting material was recovered (entries 2–4).[81] Running the reaction at 320 °C provided the product in very good yield. While the use of a sand-bath to reach such high temperatures was quite difficult (entry 6), the handling of a "Luftbad" [82] was very convenient (entry 7). Subsequent Negishi cross-coupling afforded the final naphthol **I.68**.



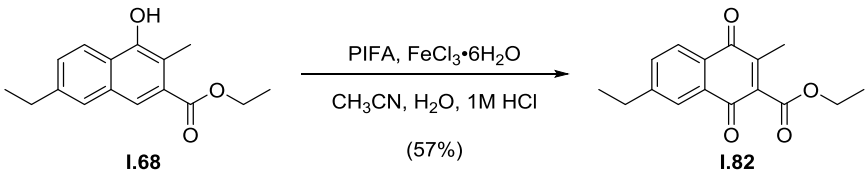
Scheme 11 Synthesis of naphthol **I.68**.

The ensuing task was to dearomatize the phenolic ring of the naphthol. Our first idea to achieve this was to oxidize the naphthols to the 1,4-naphthoquinones and introduce then an allyl or vinyl side chain by 1,4-addition. The first step, the oxidation of substrate **I.68** with PIFA and $FeCl_3$, is depicted in Scheme 12 and gave the corresponding naphthoquinone **I.82** in 57% yield.[83]

Table 3 Screening of conditions for the fragmentation reaction of **I.80**.



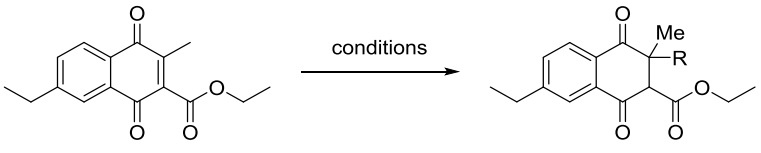
entry	conditions	result
1	190 °C, sulfolane	no reaction
2	190 °C, neat	no reaction
3	110–130 °C, allyl alcohol	no reaction
4	110–130 °C, diallylamine	no reaction
5	170 °C, microwave	no reaction
6	250– >400 °C, sand-bath	**I.81**, but: • temperature difficult to control • > 400 °C: decomposition • poor heat distribution → upscale not possible
7	320 °C, Luftbad	**I.81** (85%)



Scheme 12 Oxidation of **I.68** to the naphthoquinone **I.82**.

With **I.82** in hands, several 1,4-alkylation reagents and conditions were screened (Table 4), but unfortunately, only decomposition and unidentifiable byproducts were observed (entries 1–5).[84,85,86]

Table 4 Attempted alkylation.

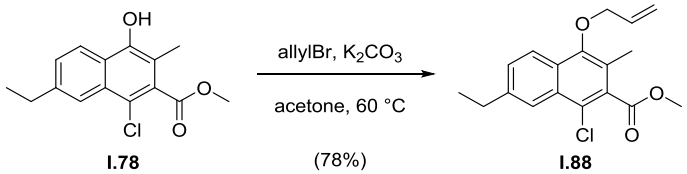


I.82 **I.83**

R = allyl, vinyl

entry	reagent	conditions	result
1	$SnBu_3$ **I.84**	$Sc(OTf)_3$, $(CH_2Cl)_2$, 50 °C,	decomposition
2	MgBr **I.85**	Et_2O, 0 °C, 2 h	decomposition
3	MgBr **I.86**	CuI, Et_2O, −30 °C, 2 h	decomposition
4	$SiMe_3$ **I.87**	TBAF, HMPA, DMF, 23 °C, 30 min	decomposition
5	$SiMe_3$ **I.87**	$TiCl_4$, CH_2Cl_2, −30 °C, 2 h	**I.82** and unidentifiable byproducts

Since the *para*-quinone approach turned out to be unsuccessful, a different strategy was elaborated. This time, we planned to dearomatize the 1-naphthols by generating the quaternary center at the C2-position. To implement this, we went for the *ortho*-Claisen rearrangements of allyl naphthol ethers. We decided to use the chlorinated naphthol **I.78** for this reaction, since the substituent at the *para*-position should prevent or at least hinder a subsequent Cope rearrangement after the Claisen rearrangement. The allyl ether **I.88** for this reaction was synthesized by the reaction of **1.78** with allyl bromide and potassium carbonate in 78% yield (Scheme 13).



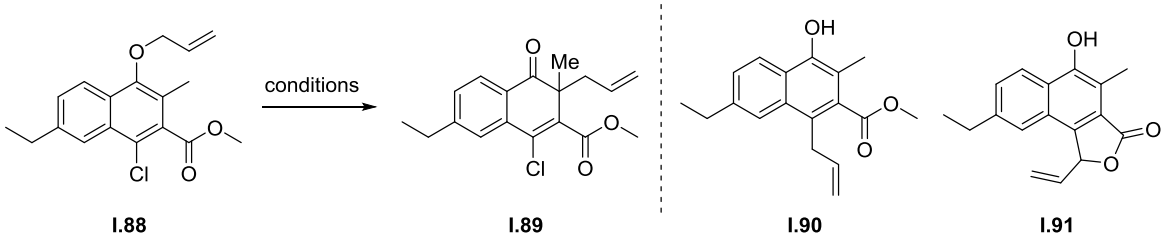
I.78 **I.88**

Scheme 13 Synthesis of allyl naphthyl ether **I.88**.

With allyl naphthyl ether **I.88** in hands, different conditions were screened for the *ortho*-Claisen rearrangement (Table 5). The reactions were carried out either in sulfolane, mesitylene or neat and at 190 or 120 °C, respectively (entries 1–5). The obtained products for all reactions were

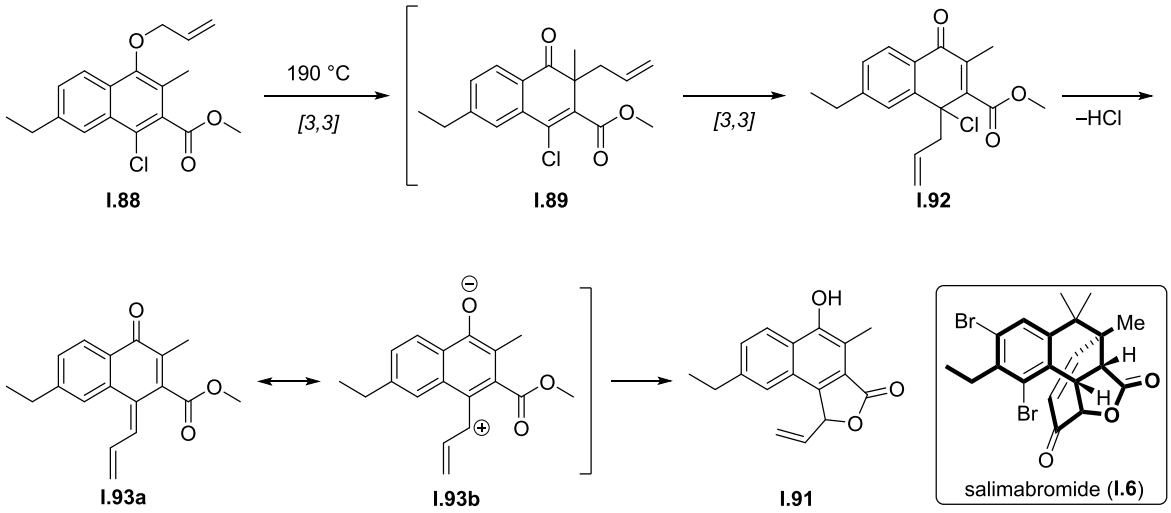
identified as **I.90** and **I.91**. The para allylated naphthol **I.90** must be generated via a tandem Claisen-Cope rearrangement, whereupon the chloride must have been eliminated. An explanation for this result was found during the analysis of the other product, the tricyclic lactone **I.91**. We propose that its formation is initiated by a thermal Claisen rearrangement (Scheme 14), whereupon the molecule undergoes a Cope rearrangement to unstable chloride **I.92**. Hydrogen chloride elimination forms *para*-quinone methide **I.93**, which is attacked by the adjacent ester to form the lactone moiety.[68] Via this unanticipated cascade reaction three of the four rings of the final natural product were formed correctly and the only missing cycle was the one of the cycloheptenone. Thus, we tried to optimize the reaction in such a manner that the lactone formation is favored; however, the best obtained yield of **I.91** was only 31% (entry 6). In addition, the observation of both products **I.90** and **I.91** indicate that the chloride at the *p*-position has no effect on the equilibrium of the tandem Claisen-Cope reaction.

Table 5 Various conditions for the envisioned *ortho*-Claisen rearrangement.



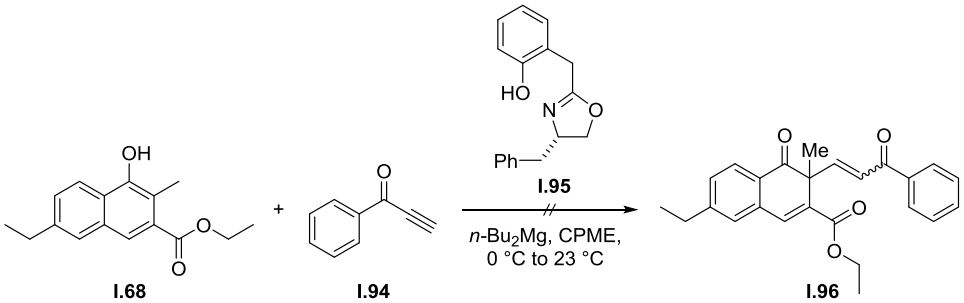
I.88 **I.89** **I.90** **I.91**

entry	conditions	result
1	sulfolane, 120 °C	**I.90** and **I.91**
2	sulfolane, 190 °C	**I.90** (10%) and **I.91** (18%)
3	mesitylene, 120 °C	**I.90**
4	neat, 120 °C	**I.90** and **I.91**
5	neat, 190 °C, 5 min	**I.90** (25%) and **I.91**
6	neat, 190 °C, 2 h	**I.91** (31%)



Scheme 14 Proposed mechanism for the formation of lactone **I.91**.

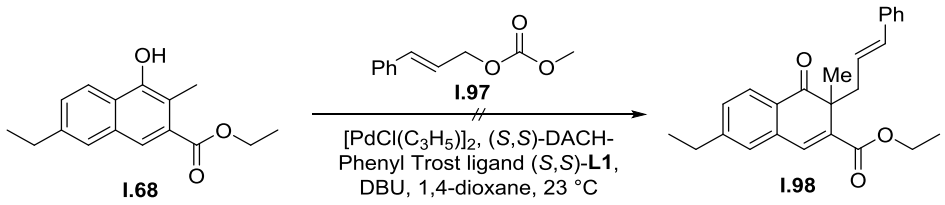
We turned therefore one more time to a different dearomatization approach and investigated a procedure, published by Wang et al. in 2015. Although, they only reported this methodology for 2-naphthols, we decided to also test it on 1-naphthol **I.68** (Scheme 15).[87] It was reported that the *Z*/*E* ratio strongly depends on the quality of the Bu_2Mg solution. Older Bu_2Mg solutions lowered the *Z*/*E* ratio of the product, but had no influence on the obtained *ee* values. Since the *Z*/*E* ratio is inconsequential for our substrate we did not care about the age of the Bu_2Mg solution. Nevertheless, the envisaged product **I.96** could not be observed.



Scheme 15 Attempted intermolecular dearomatization of 1-naphthol **I.68**.

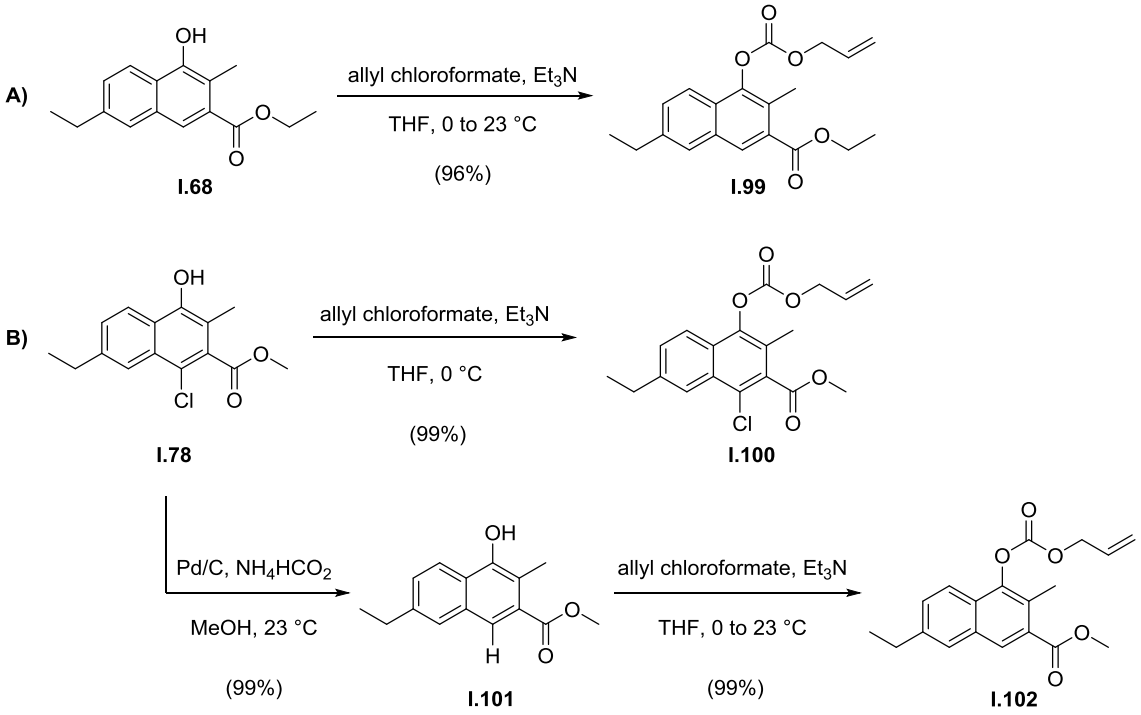
Our following idea was then to test an intermolecular dearomatization following a procedure of You from 2013.[72] He reported the use of cinnamyl carbonate **I.97**[88] in combination with DBU, a Pd(II) source and chiral Trost ligand (*S*,*S*)-**L1** for the enantioselective dearomatization of

2-naphthols. Subjecting our 1-naphthol **I.68** to these conditions gave only traces of the envisioned product **I.98**.



Scheme 16 Attempted asymmetric dearomatization via decarboxylative allylation.

Another idea to dearomatize our 1-naphthols was to perform a catalytic asymmetric dearomatization (CADA) reaction, according to the intramolecular decarboxylative Tsuji allylations.[89,90,91,92,93] The allyl carbonates **I.99**, **I.100** and **I.102** were prepared with allyl chloroformate in excellent yields (Scheme 17A and B). At this point, we also decided to simplify the synthesis of the non-halogenated naphthol by simple dehalogenation of chlorinated naphthol **I.78**.

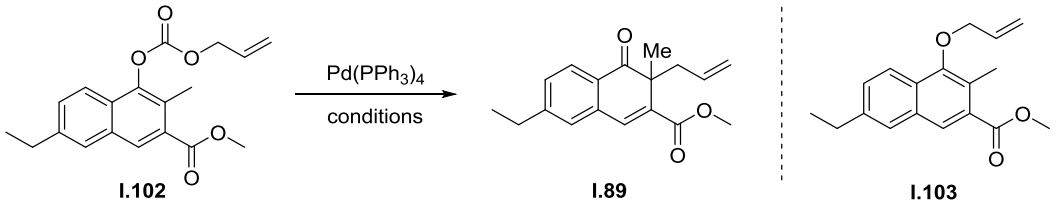


Scheme 17 Synthesis of the dearomatization precursors **I.199**, **I.100** and **I.102**.

With these substrates in hand, various conditions for the CADA reaction were screened. We started with the non-halogenated substrate **I.102** and a selection of the tested conditions is

reported in Table 6. We were pleased to obtain the dearomatized product **I.89** in over 80% yield (entry 1). Unfortunately, this result could not be obtained on larger scale (entry 2). Both reactions were stirred at 23 °C previously to heating to 45 °C, since we initially thought that this would give slightly better results. Switching the solvent from THF to toluene afforded the product in 66% yield (entry 3). Next, the solvent was changed back to THF, but this time, the whole reaction mixture was degassed right after the addition of all components (entries 4–6). The measure was taken to remove the generated CO_2 from the reaction mixture and to assure that the CO_2 did not influence the reaction in any way. Monitoring the reaction by TLC showed that the decarboxylation of the carbonate **I.102** occurred rapidly. The first new spot on TLC turned out to be *O*-allylated naphthol **I.103**, which was also observed as a side-product for all reactions. This could be the explanation for the slightly better yields when the reaction mixture was previously stirred at 23 °C for 5 min compared to the results of directly heating to elevated temperatures. However, all the listed results were inconsistent and sometimes not reproducible.

Table 6 Screening of conditions for the dearomatization of **I.102**.

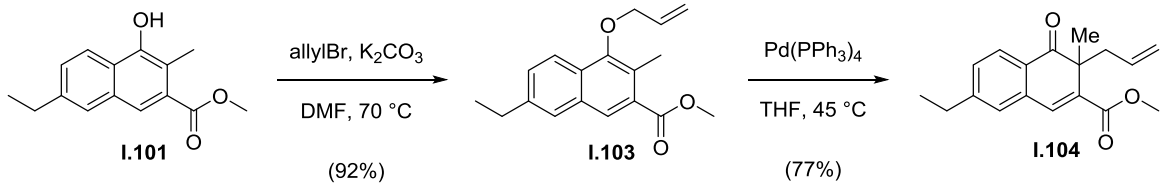


entry	solvent	T / t	comment	yield
1	THF	23 °C / 5 min 45 °C / 2.5 h	0.0305 mmol	82%
2	THF	23 °C / 5 min 45 °C / 18 h	0.152 mmol	37%
3	toluene	23 °C / 5 min 45 °C / 2.5 h	-	66%
4	THF	45 °C / 2 h	degassed reaction mixture	50%[a]
5	THF	45 °C / 40 min	degassed reaction mixture	87%[a]
6	THF	23 °C / 45 min 45 °C / 15 min	degassed reaction mixture	58%[a]

[a] determined by ^{1}H NMR ($CDCl_3$, 400 MHz; mesitylene as internal standard).

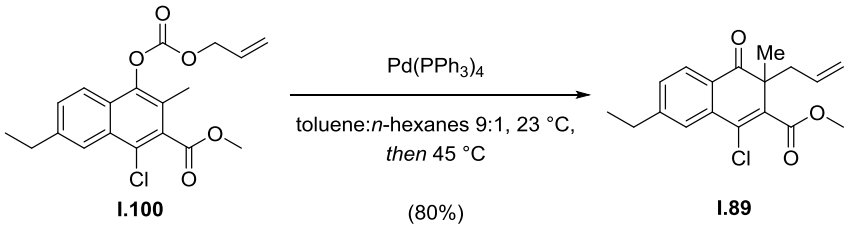
During parallel studies to investigate this intramolecular Pd-catalyzed dearomatization reaction of 1-naphthols further as a general methodology (for further information see Chapter II), a ^{1}H NMR experiment was undertaken. This clearly revealed that the decarboxylation occurred rapidly and that the first generated product is the allyl naphthyl ether, which then undergoes a Pd-catalyzed rearrangement toward the dearomatized product.[94]

Based on these results, we decided to directly synthesize allyl ether **I.103** by allylation of naphthol **I.101** (Scheme 18). Treatment of **I.103** with $Pd(PPh_3)_4$ in THF gave - as anticipated - the dearomatized product **I.104** in 77% yield. This time, the reaction was fully reproducible, even on larger scale.



Scheme 18 Dearomatization of naphthol **I.101**.

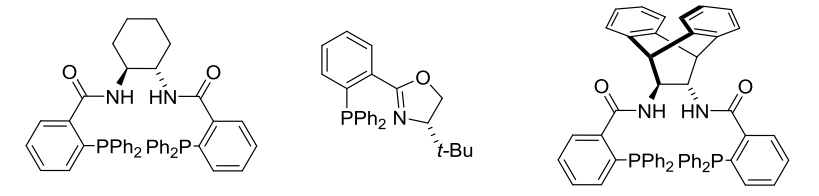
In parallel to the screening for the dearomatization of **I.101** (Table 6), an extensive screening was performed for the chlorinated substrate **I.100** as well. The final outcome was that the best yield for this transformation was achieved in a mixture of toluene and *n*-hexane in a ratio of 9 : 1 (Scheme 19).



Scheme 19 Dearomatization of **I.100**.

With the third substrate, the non-halogenated ethyl ester **I.99**, the dearomatized product **I.105** was received in 69% yield with $Pd(PPh_3)_4$ in THF at 45 °C (Table 8, entry 1). The next aim was to perform the reaction in an asymmetric fashion. For this purpose and in accordance with the literature, we changed the source of palladium to $Pd_2(dba)_3$, the solvent to toluene and the

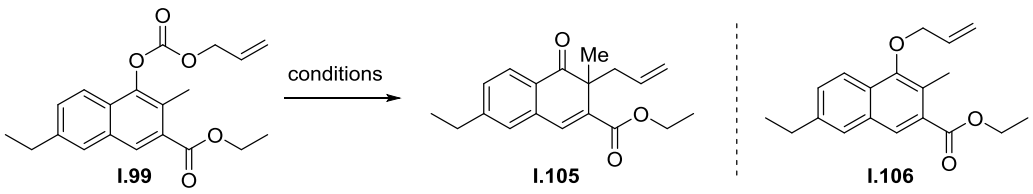
reaction temperature to 23 °C. We started the screening of the most common ligands for this reaction, which are the (*S*,*S*)-DACH-Phenyl Trost ligand (*S*,*S*)-**L1**, the (*S*)-*t*-Bu-PHOX ligand (*S*)-**L2** and the (*S*,*S*)-ANDEN-Phenyl Trost ligand (*S*,*S*)-**L3** (Scheme 20).[95,96,97,98,169]



Scheme 20 Chiral ligands (*S*,*S*)-**L1**, (*S*)-**L2** and (*S*,*S*)-**L3**.

The best result was observed with (*S*,*S*)-**L1**, affording **I.105** (32%) with 56% reisolated 1-naphthol **I.68** (entry 2). The other two ligands gave **I.105** in 17% and 25% yield and each time over 50% yield of the *O*-allylated product **I.106**. Due to the relatively low yields of the enantioselective reactions in comparison with the racemic one, we decided to carry on with the racemic dearomatization.

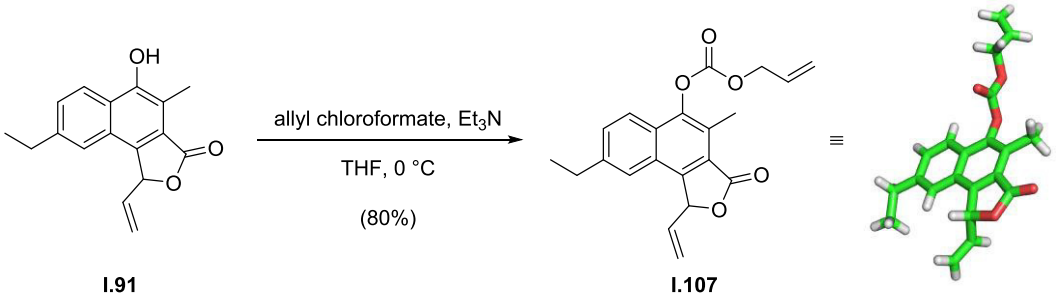
Table 7 Screening of conditions for the CADA reaction of allyl carbonate **I.99**.



entry	Pd source	ligand	solvent	T [°C] / t [h]	result[a]
1	$Pd(PPh_3)_4$ (10 mol%)	-	THF (0.03 M)	45 / 3	**I.105** (69%)[b],[c]
2	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (10 mol%)	toluene (0.03 M)	23 / 17.5	**I.105** (32%) **I.68** (56%)
3	$Pd_2(dba)_3$ (5 mol%)	(*S*)-**L2** (10 mol%)	toluene (0.03 M)	23 / 8.5	**I.105** (17%) **I.106** (52%)
4	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L3** (10 mol%)	toluene (0.03 M)	23 / 17	**I.105** (25%) **I.106** (50%)

[a] determined by ^1H NMR ($CDCl_3$, 400 MHz; mesitylene as internal standard.; [b] isolated yield; [c] the reaction was carried out on a 0.266 mmol scale.

We then turned our attention to the advanced tricyclic lactone **I.91** and tested the previously established conditions for the dearomatization of this substrate. The first step was again the formation of the allyl carbonate with allyl chloroformate to afford **I.107** in 80% yield. Crystallization from dichloromethane afforded suitable crystals for X-ray crystallography.

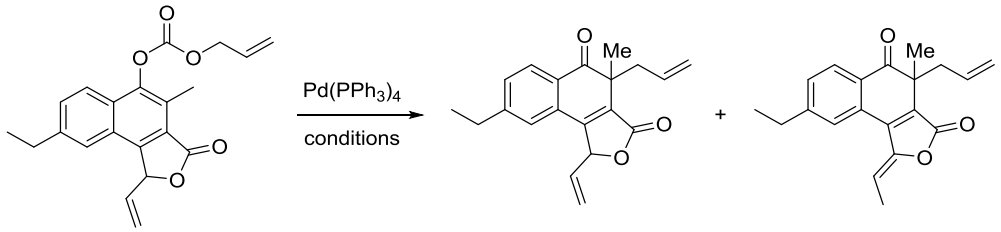


I.91 **I.107**

Scheme 21 Synthesis and crystal structure of carbonate **I.107**.

We then started to screen for the optimal conditions for the allylic dearomatization of **I.107**. The first reaction with the elaborated conditions of Table 6 resulted in the formation of only 14% yield of **I.108a+b** (entry 1). With different ratios of toluene and *n*-hexane the product was obtained as a mixture of isomers (entries 2–4), which were separated by flash column chromatography. However, it was not possible to determine the relative stereochemistry of the two diastereomers by NMR spectroscopy and suitable crystals for X-ray crystallography were not obtained. In entry 5, the substrate **I.107** was added dropwise to a solution of $Pd(PPh_3)_4$ in toluene/*n*-hexane, but the observed product **I.108** contained an isomerized vinyl group. In entries 6 and 7, the reaction mixtures were stirred first at 23 °C for a few minutes before they were heated to 45 °C. The same procedure was described previously for Table 6. The intention was to quantitatively form the allyl ether and then dearomatize it upon heating. The results seemed promising, since the product was obtained in 69% yield (combined yield of both isomers) also on larger scale (entry 8). Entries 9 and 10 were test reactions, which showed that the allyl ether is formed quantitatively at 23 °C.

Table 8 Screening of conditions for the CADA reaction of allyl carbonate **I.107**.



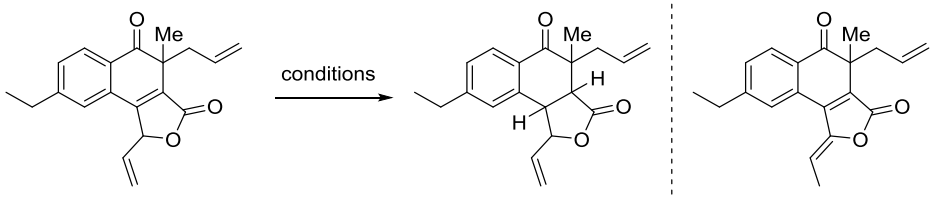
I.107 **I.108** **I.109**

entry	solvent 1	solvent 2	T [°C] / t	comment	result[a]
1	THF (0.028 M)	-	45 / 6 h		**I.108a+b** (14%) + allyl ether
2	toluene (0.038 M)	*n*-hexane (0.9 M)	45 / 15 min		**I.108a** (18%) **I.108b** (27%)
3	toluene (0.038 M)	*n*-hexane (0.38 M)	45 / 15 min	0.0284 mmol	**I.108a** (32%) **I.108b** (43%)
4	toluene (0.038 M)	*n*-hexane (0.38 M)	45 / 10 min	0.0851 mmol	**I.108a** (23%) **I.108b** (31%)
5[b]	toluene (0.038 M)	*n*-hexane (0.38 M)	45 / 10 min		**I.109**
6	toluene (0.038 M)	*n*-hexane (0.38 M)	23 / 7 min 45 / 10 min	0.0851 mmol	**I.108a** (28%) **I.108b** (37%)
7	toluene (0.038 M)	*n*-hexane (0.38 M)	23 / 4 min 45 / 10 min	0.255 mmol	**I.108a** (20%) **I.108b** (43%)
8	toluene (0.038 M)	*n*-hexane (0.38 M)	23 / 4 min 45 / 45 min	0.284 mmol	**I.108a+b** (69%)
9	THF (0.028 M)	-	23 / 6 h		allyl ether
10	toluene (0.028 M)	-	23 / 6 h		allyl ether

[a] Yields were determined from crude ^{1}H NMR; [b] Different addition mode: $Pd(PPh_3)_4$ was solved in toluene/*n*-hexane and warmed to 45 °C. The substrate was solved in toluene and added dropwise to the $Pd(PPh_3)_4$ solution.

The ensuing step was to selectively reduce the styrene subunit of **I.108** in the presence of the allylic and the vinylic alkene. The intention of this was to bring both terminal double bonds in close proximity in order to facilitate a ring-closing metathesis (RCM), which would generate the fourth cycle. For the reduction of the tetrasubstituted unsaturated lactone moiety several conditions were screened (Table 9). Unfortunately, all attempts for selective 1,4-reduction either migrated the vinyl group to give the conjugated product **I.109** (entries 1 and 4) or reduced the ketone to the corresponding secondary, benzylic alcohol (entry 3).[99,100,101] With CuCl and $NaBH_4$ in diethyl ether, no reaction took place (entry 2).[102]

Table 9 Screening of conditions for the 1,4-reduction of lactone **I.108**.

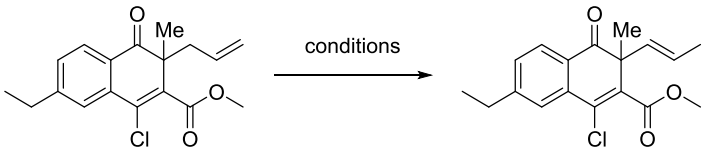


entry	metal salt	reducing agent	solvent	T [°C]	result
1	$CoCl_2$•$6H_2O$	$NaBH_4$	MeOH	23	decomposition and traces of **I.109**
2	CuCl	$NaBH_4$	Et_2O	–78	no reaction
3	CuCl	$NaBH_4$	MeOH/THF 7:4	0	ketone was reduced to the alcohol
4	-	Mg	MeOH	23	**I.109**

We then changed back to our dearomatized naphthols and continued with the migration of the *exo*-double bond (Table 10). A wide variety of catalysts in combination with several ligands and additives were tested at different temperatures. Using the conditions shown in entries 4 and 6,[103] α-tetralone **I.111** could be isolated as a mixture of double bond isomers in good yield. Unfortunately, these results could not be reproduced on larger scale (entries 5 and 7). Next, a methodology from the Nishida group was tested where they use Grubbs II in combination with vinyloxy-trimethylsilane as catalyst (entry 11).[104] With this, the *E*-isomer of **I.111** was afforded in 75% yield, but at least 20 mol% of the catalyst were required. Since these conditions are not

practical on large scale, another migration reaction, developed by Skrydstrup, was elaborated.[105] This methodology reports the use of $Pd(dba)_2$, P(*t*-Bu)$_3$ and isobutyryl chloride in a ratio of 1:1:1 to migrate or isomerize double bonds. By using these conditions, product **I.111** could be isolated in 79% yield together with remaining traces of the starting material **I.89** (entry 13).

Table 10 Screening of conditions for the migration of *exo*-double bond of **I.89**.



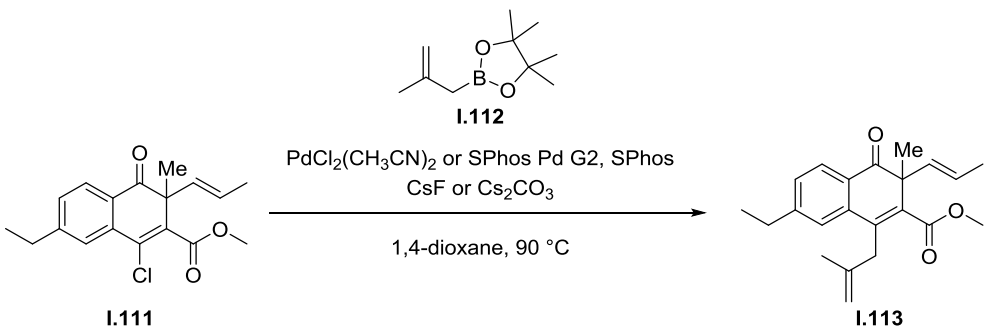
I.89 **I.111**

entry	conditions	T / t	comment	result
1	$PdCl_2(CH_3CN)_2$ (30 mol%), benzene	60 / 22.5 h	-	**I.89**
2	$PdCl_2(CH_3CN)_2$ (10 mol%), CH_2Cl_2	45 / 19 h	-	**I.89**
3	$RhCl_3 \cdot xH_2O$, EtOH	70 / 6 h	-	decomposition
4	$[Pd(allyl)Cl]_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%), AgOTf, CH_2Cl_2	23 / 21.5 h	0.0157 mmol	**I.111** (92%); d.r. = 5.6 : 1[a]
5	$[Pd(allyl)Cl]_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%), AgOTf, CH_2Cl_2	23 / 15.5 h	0.0627 mmol	**I.111** : **I.89** = 0.67 : 1
6	$[Pd(allyl)Cl]_2$ (10 mol%), P(*o*-tol)$_3$ (20 mol%), AgOTf, CH_2Cl_2	23 / 15.5 h	0.0627 mmol	**I.111** (80%); d.r. = 7.8 : 1[a]
7	$[Pd(allyl)Cl]_2$ (10 mol%), P(*o*-tol)$_3$ (20 mol%), AgOTf, CH_2Cl_2	23 / 18 h	0.188 mmol	**I.89** and traces of **I.111**
8	KHMDS, THF	23 / 5 min	-	**I.89** and decomposition
9	Grubbs II (10 mol%), MeOH	60 / 23 h	-	**I.89**
10	Grubbs II (10 mol%),	50 / 4.5 h	-	traces of **I.111**

	vinyloxyTMS, toluene			
11	Grubbs II (20 mol%), vinyloxyTMS, toluene	100 / 28 h	-	**I.111** (75%); d.r. > 99 : 1[a]
12	$Pd(dba)_2$ (5 mol%), P(*t*-Bu)$_3$ (5 mol%), isobutyryl chloride (5 mol%), toluene	80 / 37 h	-	**I.111** (72%); d.r. > 99 : 1;[a] remaining **I.89**
13	$Pd(dba)_2$ (10 mol%), P(*t*-Bu)$_3$ (10 mol%), isobutyryl chloride (10 mol%), toluene	80 / 39 h	-	**I.111** (79%); d.r. > 99 : 1;[a] remaining **I.89**
14	$Pd(dba)_2$ (10 mol%), P(*t*-Bu)$_3$ (10 mol%), isobutyryl chloride (10 mol%), toluene	80 / 41 h	1.96 mmol	**I.111** (84%); d.r. > 99 : 1;[a] remaining **I.89**

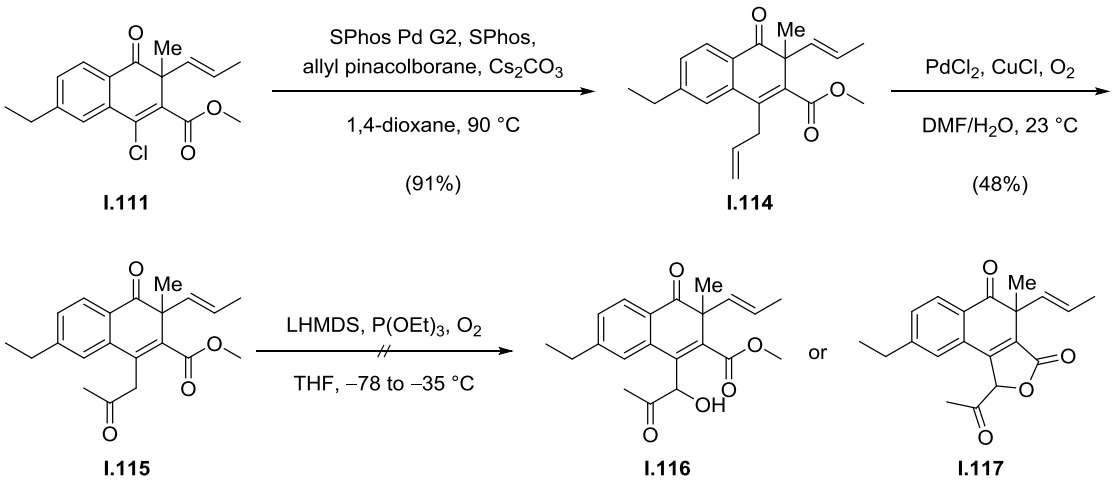
[a] d.r. (*E*/*Z*) determined by ^{1}H NMR spectroscopy.

Having successfully isomerized the allylic double bond, we concentrated on the introduction of the 2-methylallyl group at the C4-position. The idea was to couple the chloride of **I.111** via a Suzuki-Miyaura cross-coupling with boronic ester **I.112**, which was prepared according to a procedure of Singaram and co-workers.[106] In Scheme 22, the screening conditions for the coupling are depicted. It was possible to obtain the allylated product **I.113** under all reaction conditions tested, but unfortunately, the product was co-polar with the starting material **I.111** and thus made the separation and isolation of pure **I.113** impossible. In addition, we were not able to obtain full conversion of the starting material.



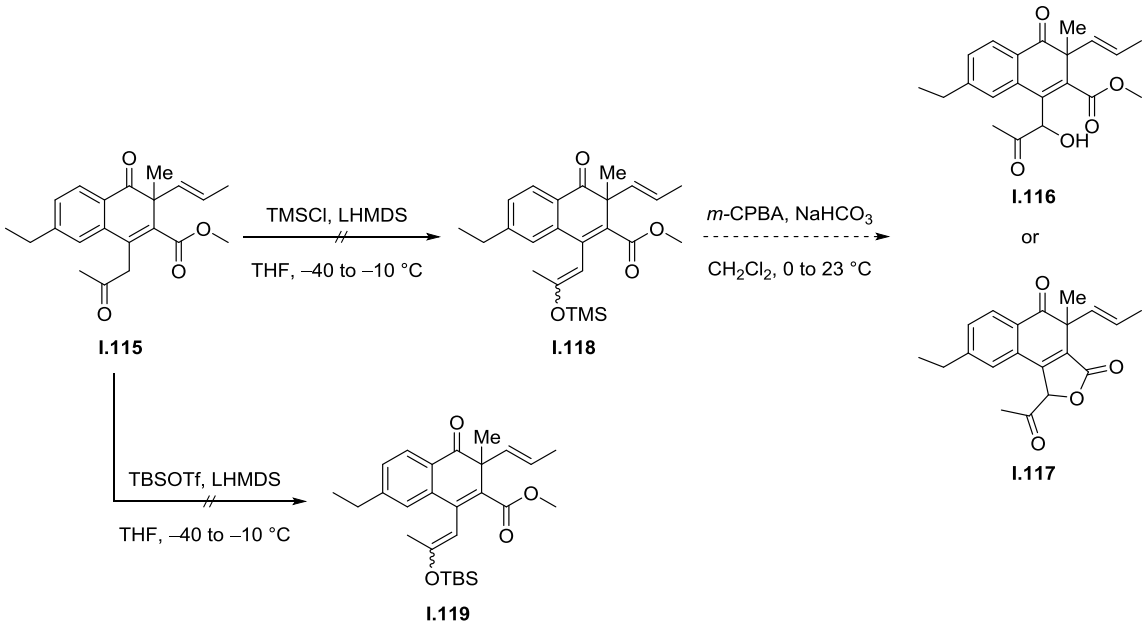
Scheme 22 Suzuki-Miyaura cross-coupling to introduce the 2-methylallyl group.

An alternative reaction was the Suzuki-Miyaura cross-coupling of **I.111** with the commercially available allyl boronic acid pinacol ester (Scheme 23). Starting material **I.111** and product **I.114** were again co-polar, but after a detailed screen of reaction conditions full conversion of the starting material could be achieved. The coupling product **I.114** could be isolated in pure form and very good yield. This substrate was then selectively oxidized by a Wacker oxidation to provide **I.115** in 48% yield. Next, the formation of lactone **I.117** was investigated. The first attempt was a direct α-hydroxylation, using LHMDS, O_2 and $P(OEt)_3$,[107] to obtain the thermodynamic product **I.116** or the already cyclized lactone **I.117**, but this failed and only decomposition was observed.



Scheme 23 Suzuki-Miyaura cross-coupling of **I.111**, followed by Wacker oxidation and attempted α-hydroxylation.

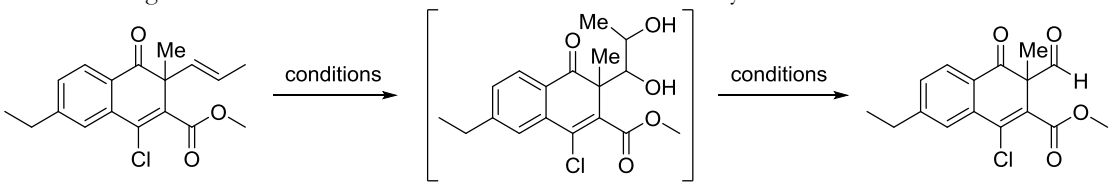
For a stepwise α-hydroxylation, the formation TMS enol ether **I.118**, followed by a Rubottom oxidation was envisaged, however even attempts to prepare the TBS enol ether **I.119** failed under these conditions (Scheme 24).



Scheme 24 Attempted stepwise α-hydroxylation.

Next, we focused on the formation of the aldehyde moiety. Therefore, the vinyl group of ketone **I.111** should be dihydroxlated first and then cleaved to yield the corresponding aldehyde **I.121**. Unfortunately, under the shown conditions either no reaction or decomposition occurred (Table 11).71[,108,109] Reasons for the decomposition might be unselective dihydroxylation of both alkenes, or a retro-aldol reaction due to the presence of the ketone moiety in β-position to the envisioned aldehyde. Lactonization reactions with the ester group are possible as well.

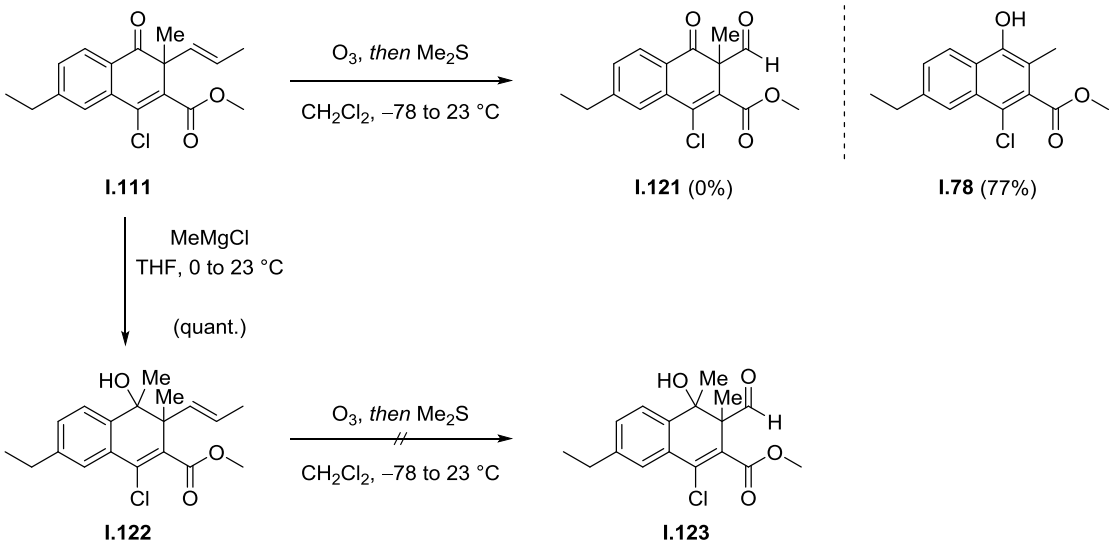
Table 11 Screening of conditions for the formation of diol **I.120** and aldehyde **I.121**.



entry	conditions	solvent	result
1	OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, DABCO	*t*-BuOH/H_2O	**I.111**
2	OsO_4, NMO, DABCO	ethylene glycol/H_2O	decomposition
3	1) $K_2[OsO_2(OH)_4]$, NMO 2) $NaIO_4$	1) H_2O/acetone 2) THF/H_2O	decomposition

Another approach to obtain the aldehyde was the ozonolysis of the vinyl group (Scheme 25). However, the ozonolysis of **I.111** resulted in the formation of naphthol **I.78** by a retro-aldol reaction, mentioned also for Table 11. To avoid this problem, the ketone was converted to tertiary alcohol **I.122** and used in another unsuccessful attempt to obtain the aldehyde via ozonolysis, but only decomposition was observed.

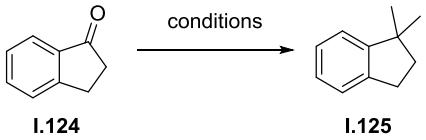
At this point, we realized that the ketone moiety vicinal to the quaternary center is the reason for many of the side-reactions. Therefore, we decided to introduce the *gem*-dimethyl group at this position first and then investigate the the aldol condensation again.



Scheme 25 Ozonolysis of ketone **I.111** and tertiary alcohol **I.122**.

We started our investigations for the conversion of the ketone into a *gem*-dimethyl group with the exhaustive methylation established by Reetz.[110] Since previous experiments with this methodology were unsuccessful due to the sensibility of the Reetz reagent, the methodology was optimized with the literature known test substrate - indanone **I.124** (Table 12). During this screening we realized that the Reetz reagent is prepared best at 0 °C[111] instead of –30 °C and that it is slightly sensitive to light. With this in mind a complete conversion of **I.124** to **I.125** could be observed (entry 4).

Table 12 Screening of conditions for the exhaustive methylation of indanone **I.124** as reported by Reetz.

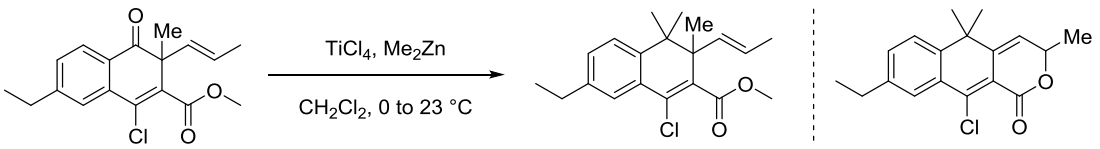


I.124 **I.125**

entry	reagents	T [°C]	scale [mmol]	result[a]
1	$TiCl_4$[b] (2.2 equiv), Me_2Zn (2.2 equiv)	–30 to 0	0.378	**I.124**
2	$TiCl_4$[c] (6 equiv), Me_2Zn (6 equiv)	–30 to 0	0.757	ratio **I.124** : **I.125** = 3.3 : 1
3	$TiCl_4$ (6 equiv), Me_2Zn (6 equiv)	0 to 23	0.757	ratio **I.124** : **I.125** = 0.8 : 1
4	$TiCl_4$ (6 equiv), Me_2Zn (6 equiv)	0 to 23	0.378	**I.125**
5	$TiCl_4$ (3 equiv), Me_2Zn (6 equiv)	0 to 23	0.378	ratio **I.124** : **I.125** = 0.8 : 1

[a] No yields were measured, since the product **I.125** was too volatile. Ratios of starting material to product were determined from crude ^{1}H NMR; [b] Neat $TiCl_4$; [c] 1 M solution of $TiCl_4$ in CH_2Cl_2.

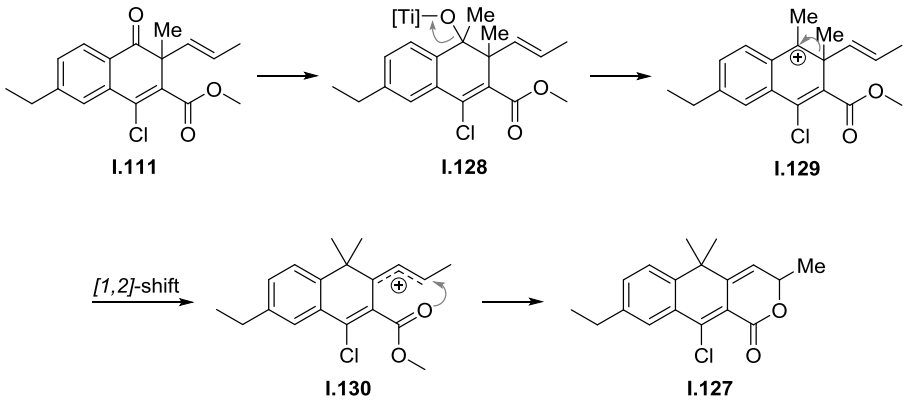
With the optimized conditions of Table 12 in hands, the direct *gem*-dimethylation of **I.111** was performed, but the observed product was identified to be the tricyclic lactone **I.127** and not the envisioned product **I.126**.



I.111 **I.126** **I.127**

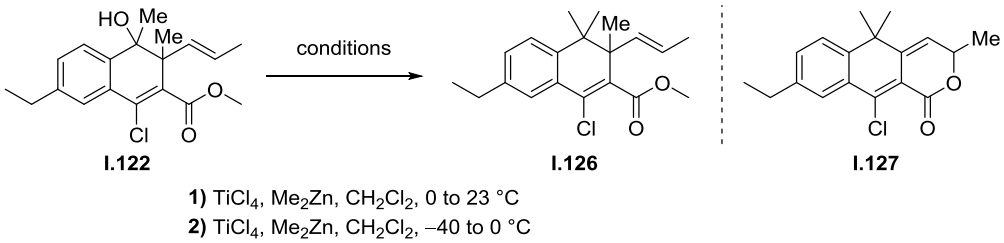
Scheme 26 Attempted exhaustive methylation of ketone **I.111**.

The proposed mechanism for the formation of **I.127** is depicted in Scheme 27. The benzylic tertiary cation **I.129** is trapped by the vicinal methyl group by a *[1,2]*-shift and the generated bis-allylic cation **I.130** is in turn trapped by the ester.



Scheme 27 Proposed mechanism for the formation of **I.127**.

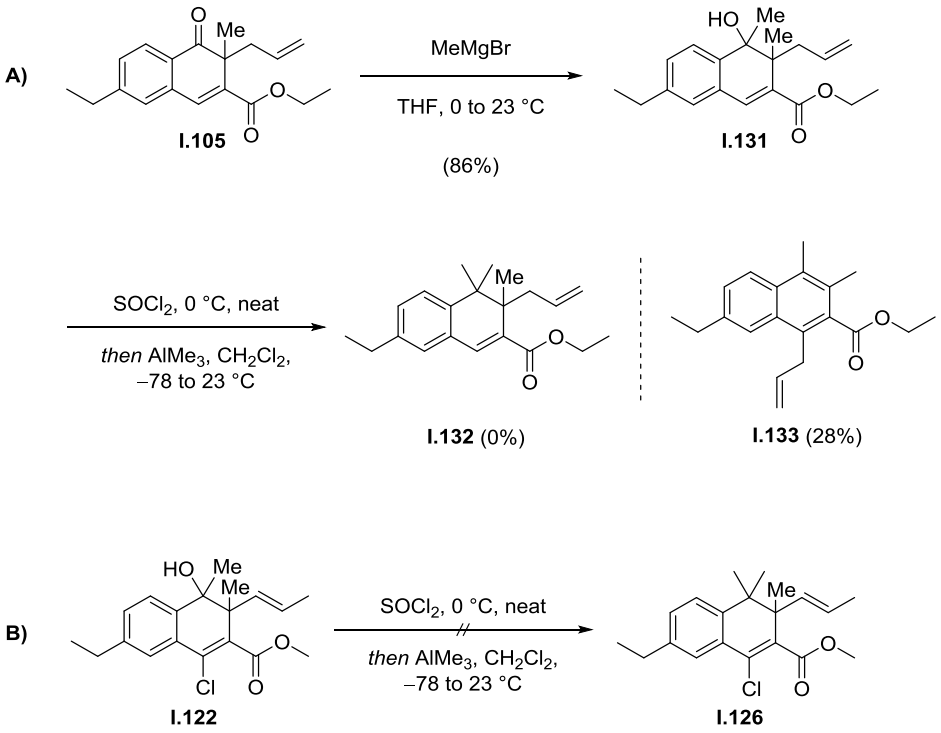
Since Reetz also reported two-step *gem*-dimethylation reactions starting from tertiary alcohols,[110] we investigated this approach as well (Scheme 28). However, the observed product was again the one from the unwanted *[1,2]*-shift.



Scheme 28 Conditions for the methylation of tertiary alcohol **I.122**.

Another idea was to perform a two-step synthesis for the *gem*-dimethylation by a procedure of Carlier.[112] The first step was the formation of tertiary alcohol **I.131** (Scheme 29). Afterwards, the benzylic alcohol was treated with $SOCl_2$. Carlier and co-workers reported that first a chlorosulfite intermediate is generated, which ionizes into a stabilized carbocation/chlorosulfite ion pair, which forms subsequently the tertiary chloride under elimination of SO_2. Subsequent addition of $AlMe_3$ to this crude reaction mixture should then introduce the methyl group. However, the only isolated product was the rearomatized Cope rearrangement product **I.133** (Scheme 29A). To prevent this rearrangement, substrate **I.122**, containing a vinyl instead of an

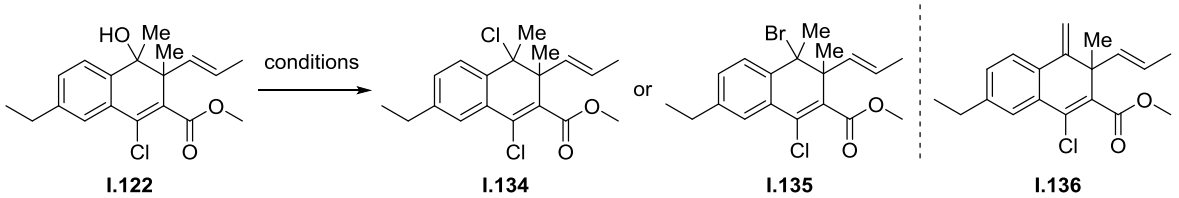
allyl group, was subjected to the same conditions, but only a complex mixture could be observed (Scheme 29B).



Scheme 29 Attempted stepwise *gem*-dimethylation of **I.131** and **I.122** with $SOCl_2$ and $AlMe_3$.

Inspired by the idea of generating the tertiary chloride as intermediate, we next tried to isolate such a halide (Table 13). Unfortunately, only decomposition or the formation of a complex mixture could be observed with $SOCl_2$ as reagent (entries 1–3).[112] Using $MgBr_2{\cdot}Et_2O$ and TBAB, only afforded alkene **I.136** (entry 4).[113]

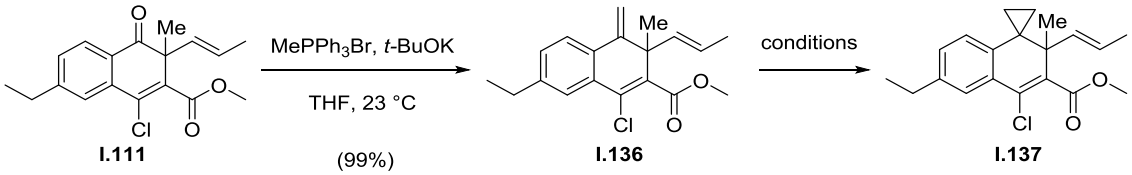
Table 13 Screening of conditions to convert tertiary alcohol **I.122** into tertiary halide **I.134** or **I.135**.



entry	reagents	solvent	result
1	$SOCl_2$, pyridine	CH_2Cl_2	complex mixture
2	$SOCl_2$, pyridine	-	decomposition
3	$SOCl_2$	-	complex mixture
4	$MgBr_2{\cdot}Et_2O$, TBAB	CH_2Cl_2	**I.136**

Another approach was to form a cyclopropane ring at the position of the ketone, which could then be reduced to the *gem*-dimethyl group. The formation of the alkene **I.136** by a Wittig olefination was the first step and gave the product in very good yield (Table 14). With this alkene, various conditions for the ensuing Simmons-Smith cyclopropanation were screened. However, this reaction turned out to be very challenging. With $(ClCH_2)_2Zn$, prepared from Et_2Zn and CH_2ICl, no reaction took place at all (entry 1).[114,115] Using Et_2Zn/CH_2I_2 instead did not change the reaction outcome, even when a large excess of reagents was used (entries 2–4). In a publication from 2003, Shi and co-workers report the in situ formation of a $CF_3CO_2ZnCH_2I$ complex, which is part of a class of tunable zinc reagents. However, no conversion could be observed with this reagent either (entries 5 and 6).[116] Another idea was to subject the reaction mixture to ultra high pressure (14 kbar), but this was again not successful (entry 7). Subsequently, we changed from Et_2Zn to Zn/Cu and Zn/Ag couple[117,118] (entries 8–12). However, this time only the starting material and a complex mixture were isolated.

Table 14 Screening of conditions for the Simmons-Smith cyclopropanation of **I.136**.

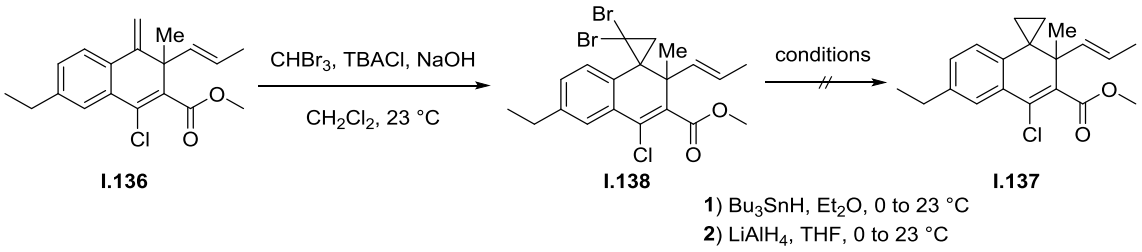


I.111 I.136 I.137

entry	reagents	additive	solvent / T [°C]	t	result
1	Et_2Zn (1.2 equiv), CH_2ICl (2.4 equiv)	-	CH_2Cl_2 / 0 to 23	4 h	**I.136**
2	Et_2Zn (2 equiv), CH_2I_2 (2.1 equiv)	-	CH_2Cl_2 / 23	8 h	**I.136**
3	Et_2Zn (2.5 equiv), CH_2I_2 (5 equiv)	-	1,2-dichloroethane / 60	27 h	**I.136**
4	Et_2Zn (15 equiv), CH_2I_2 (30 equiv)	-	CH_2Cl_2 / 23	27 h	**I.136**
5	Et_2Zn (2 equiv), CH_2I_2 (2.1 equiv)	TFA (2.2 equiv)	CH_2Cl_2 / 0 to 23	2 h	**I.136**
6	Et_2Zn (4 equiv), CH_2I_2	TFA (4 equiv)	CH_2Cl_2 / 23	5 d	**I.136**

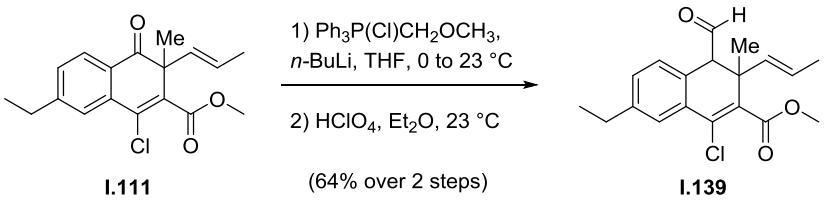
	(4 equiv)				
7	Et_2Zn (4 equiv), CH_2I_2 (4 equiv)	TFA (4 equiv)	CH_2Cl_2 / 20; 14 kbar	18 h	**I.136**
8	Zn/Ag (100 equiv), CH_2I_2 (16 equiv)	-	Et_2O / 60	25 h	**I.136**
9	Zn/Ag (100 equiv), CH_2I_2 (16 equiv)	-	Et_2O / 60	2 d	**I.136** + complex mixture
10	Zn/Ag (200 equiv), CH_2I_2 (30 equiv)	-	Et_2O / 60	2 d	complex mixture
11	Zn/Cu (30 equiv), CH_2I_2 (30 equiv)	I_2 (cat.)	Et_2O / 50	4 d	**I.136** + complex mixture
12	Zn/Cu (30 equiv), CH_2I_2 (30 equiv)	-	Et_2O / 50	4 d	**I.136** + complex mixture

Since the Simmons-Smith cyclopropanation reaction did not give any satisfying results, we decided to test a *gem*-dihalocyclopropanation. However, we were not sure, if the obtained product was the desired cyclopropane **I.138**, since clean purification could not be carried out (Scheme 30).[119] Attempted dehalogenation with the impure material using either Bu_3SnH or $LiAlH_4$ was not successful.



Scheme 30 *Gem*-dihalocyclopropanation of **I.136** and attempted reduction to cyclopropane **I.137**.

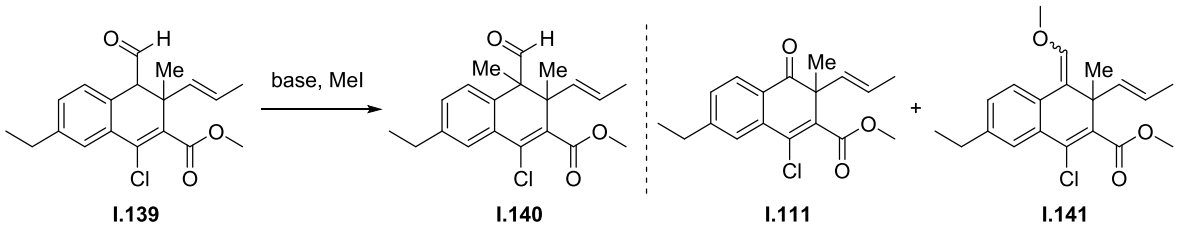
Since all the methods to install the *gem*-dimethyl group in a more or less direct way failed, we envisaged a quite different approach. The ketone functionality of **I.111** was transferred into aldehyde **I.139** by a Kluge-Wittig reaction and subsequent deprotection (Scheme 31).[120]



Scheme 31 Formation of the aldehyde **I.137**.

The ensuing step was the alkylation at the α-position of aldehyde **I.139** to form the second quaternary center, which should afterwards be converted into the *gem*-dimethyl group. We started the screening with the most commonly used conditions, by treating **I.139** with LHMDS and MeI afterwards (entry 1). To our surprise, the obtained product turned out to be ketone **I.111**. Changing to *t*-BuOK or Cs_2CO_3 gave either ketone **I.111** again (entries 2 and 3), just starting material **I.139** (entry 4), or a complex mixture (entry 5). With NaH and a large excess of MeI (entry 7), product **I.140** could be isolated the first time, but with relatively large amounts of *O*-alkylated aldehyde **I.141** as side product. Lowering the temperature (entry 8) only resulted in the formation of the deformylation product **I.111** again. A literature survey revealed that similar reactions are known with molecular oxygen.[121,122] Therefore, the conditions of entry 7 were tested again, but this time the reaction mixture containing solvent, substrate and MeI was carefully degassed before it was added to NaH (entry 9). Applying these conditions, **I.140** was isolated in 69% yield without significant byproducts. An idea to improve the reaction even further was to use KH instead of NaH (entries 10 and 11), but unfortunately only **I.141** was observed.

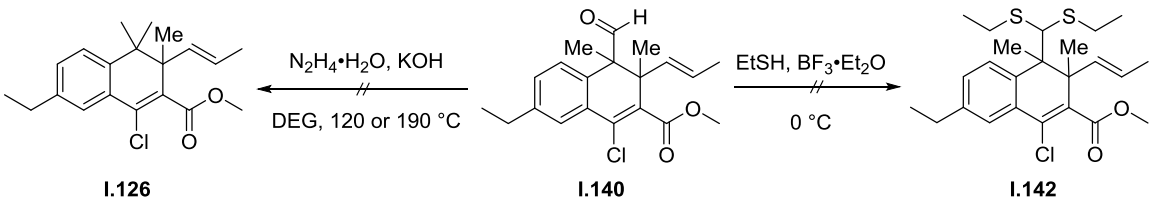
Table 15 Screening of conditions for the alkylation of aldehyde **I.139**.



entry	base	solvent / T [°C]	result
1	LHMDS	THF / −65 to 23	**I.111**
2	*t*-BuOK	THF/*t*-BuOH / −78 to −15	**I.111**
3	*t*-BuOK	THF / 0 to 23	**I.111**
4	*t*-BuOK	THF/*t*-BuOH / −78	**I.139**
5	Cs_2CO_3	1,4-dioxane / 23	complex mixture
6	NaH[a]	THF / 0 to 23	**I.111**
7	NaH[b]	THF / 0 to 23	**I.140** (54%), **I.141** (22%)
8	NaH	THF / −35 to 23	**I.111**
9[c]	NaH	THF / 0 to 23	**I.140** (69%)
10[c]	KH	THF / 0	**I.141**
11[c]	KH	THF / 23	**I.141**

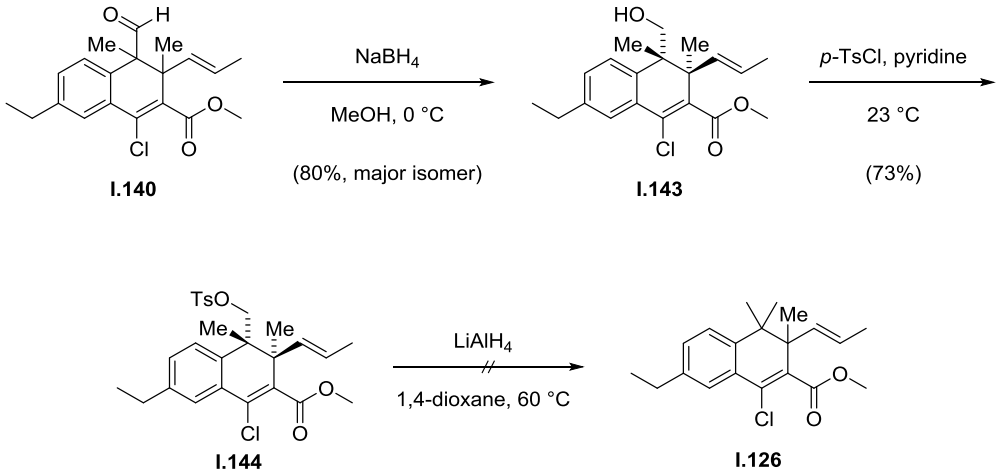
[a] NaH (2 equiv) and MeI (2 equiv) were used; [b] NaH (2 equiv) and MeI (10 equiv) were used; [c] the reaction mixture of **I.139**, MeI and solvent was thoroughly degassed by freeze-pump-thaw.

Therefore, we stayed with the conditions of entry 9 and carried on. The next step was the conversion of the aldehyde into a methyl group. Our first idea was to perform a Wolff-Kishner reduction (Scheme 32), but only decomposition of the starting material **I.140** could be observed.[123] Another idea was to form thioacetal **I.142** from aldehyde **I.140** and convert this into a methyl group by treatment with Raney nickel. However, thioacetal **I.142** could never be synthesized.[124]



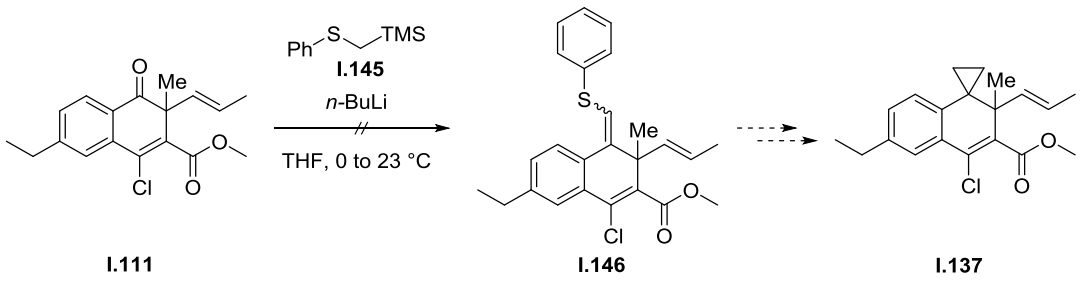
Scheme 32 Attempted Wolff-Kishner reduction and thioacetal formation of **I.140**.

Since both attempts were not successful, aldehyde **I.140** was reduced to alcohol **I.143** followed by separation of both diastereomers by flash column chromatography (Scheme 33). Subsequent tosylation afforded **I.144**, which was treated with excess $LiAlH_4$ at 60 °C, but even after stirring for 18 h only starting material **I.144** was observed. Not even the ester moiety was reduced by these conditions.



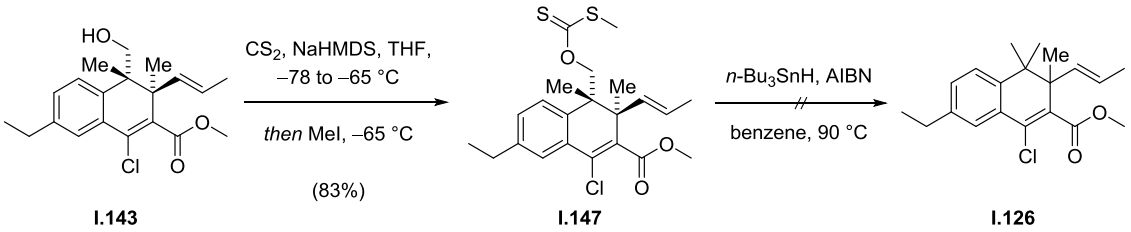
Scheme 33 Formation of tosylate **I.144** and attempted reduction of the primary tosylate.

A different strategy to introduce the *gem*-dimethyl group was to perform a Peterson olefination with ketone **I.111**, followed by a Simmons-Smith cyclopropanation and subsequent treatment with Raney nickel to get **I.137**. However, the product of the Peterson olefination with sulfide **I.145**[125] could not be obtained (Scheme 34).



Scheme 34 Attempted Peterson olefination to form alkene **I.146**.

Lastly, a Barton-McCombie deoxygenation was envisaged to remove the neopentylic hydroxyl group. Thus, xanthate **I.147** was prepared according to a typical procedure and was provided in very good yield (Scheme 35). Subjecting it to the deoxygenation conditions afforded however only decomposition.



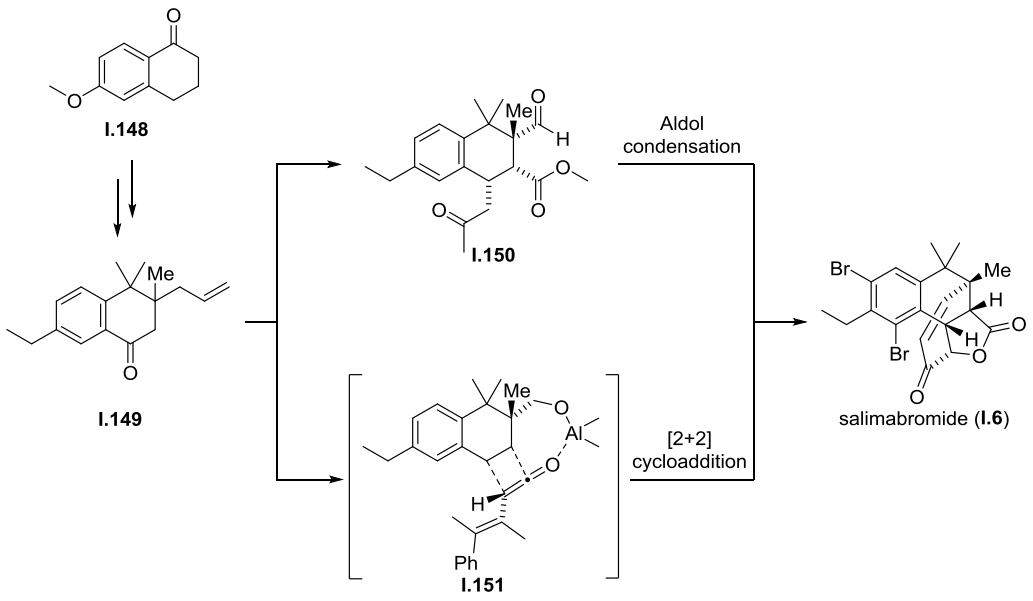
I.143 **I.147** **I.126**

Scheme 35 Attempted Barton-McCombie deoxygenation of **I.143**.

2.2 Second Generation Approach

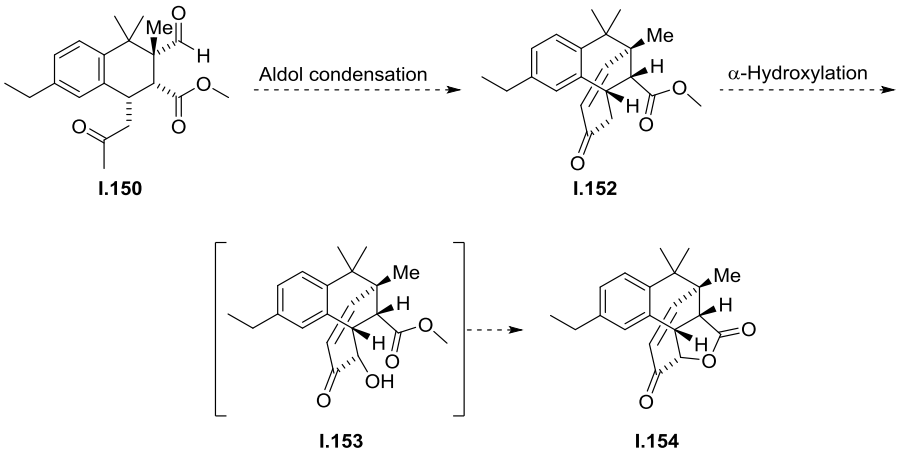
2.2.1 Synthesis of a Common Precursor for the Aldol Condensation Approach and the [2+2] Cycloaddition Approach

Since the synthesis of the intermediates **I.89** and **I.104** was getting more and more unlikely, due to serious problems with the introduction of the second quaternary center, the *gem*-dimethyl group, we decided to explore a completely new synthetic approach to reach the core structure. A short retrosynthetic analysis is depicted in Scheme 36. The plan was to start with the 6-methoxy-1-tetralone (**I.148**) and form the intermediate **I.149**. Based on this, two approaches for the key step were intended (Scheme 36): an Aldol condensation – similar to the previously planned key step – and a [2+2] cycloaddition.



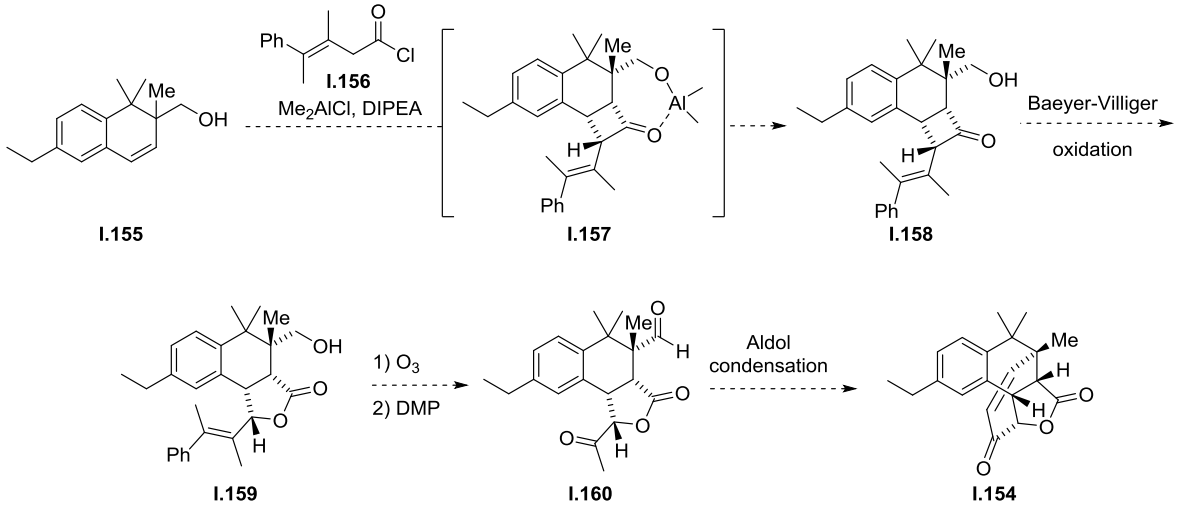
Scheme 36 Cyclization precursors **I.150** and **I.151** based on intermediate **I.149**.

The Aldol condensation with **I.150** would give the tricyclic substrate **I.152**, which has the cycloheptenone ring right in place (Scheme 37). Subsequent α-hydroxylation next to the unsaturated ketone would afford alcohol **I.153**, which should immediately cyclize to the γ-butyrolactone moiety.



Scheme 37 Aldol condensation approach.

The envisaged [2+2] cycloaddition approach is depicted in Scheme 38. Starting from neopentylic alcohol **I.155**, we wanted to use the protocol of Brown and Rasik, who reported ketene-alkene [2+2] cycloadditions, promoted by Lewis acids, with in situ generated alkenyl ketenes. Those alkenyl ketenes are very reactive and tend to undergo [4+2] cycloadditions with itself. Therefore, the alkene substrate has to be used in excess.[126] A second challenge for this step was that the cycloaddition had to occur from the side of the alcohol. To accomplish this, we wanted to use the aluminium alkoxide to coordinate to the ketene (**I.157**) and thus direct the cycloaddition. This should be feasible, since the required Lewis acid for the cycloaddition is $AlMe_3$ or a variant thereof. After the addition, the cyclobutanon should be transformed into the lactone **I.159** by a Baeyer-Villiger oxidation.[126] Subsequent ozonolysis of alkene mojety of **I.159**, followed by oxidation of the alcohol would lead to **I.160**, which then cyclizes to **I.154** via an intramolecular aldol condensation.

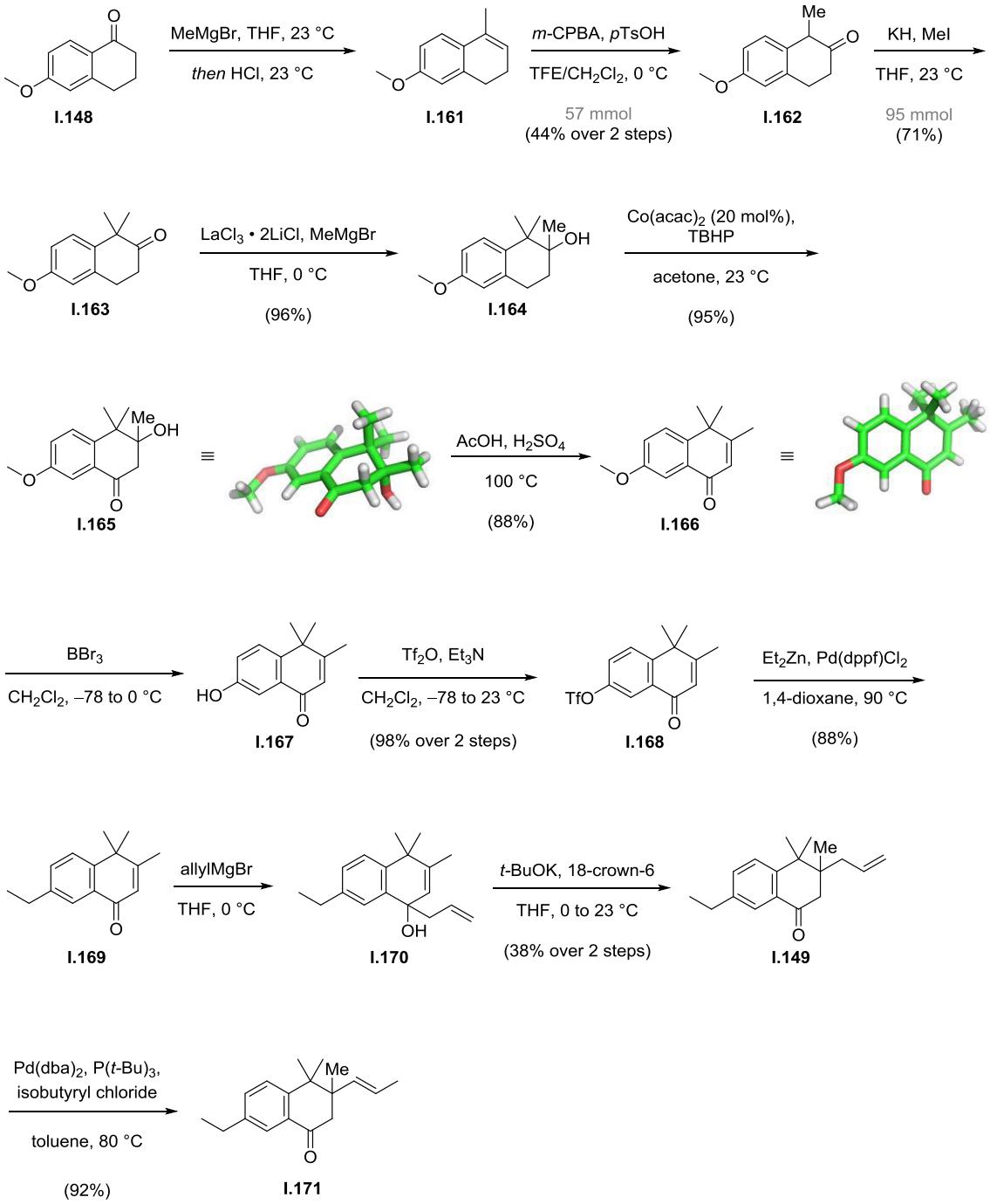


Scheme 38 [2+2] Cycloaddition approach.

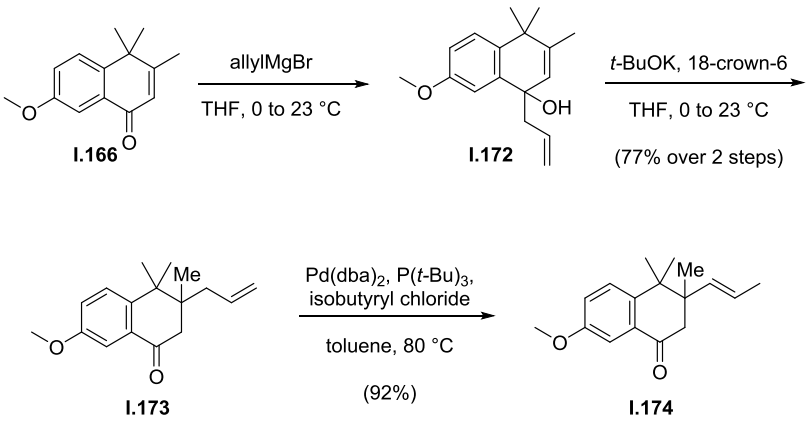
The synthesis of the common intermediate **I.149** started with the 1,2-addition of MeMgBr to **I.148**, followed by the elimination of the tertiary alcohol under acidic conditions (Scheme 39).[127] Epoxidation and subsequent Meinwald rearrangement[128] afforded β-tetralone **I.162**, which was alkylated with KH and MeI.[129] For this reaction, careful degassing of the solvent together with the substrate was mandatory since otherwise α-hydroxylation of the benzylic position took place. Interestingly, the alkylation did not work at all with NaH as base. A second 1,2-addition of MeMgBr to **I.163** - activated by lanthanum(III) chloride bis(lithium chloride) complex solution ($LaCl_3 \cdot 2LiCl$)[130] - followed by benzylic oxidation[131] and elimination[132] of the tertiary alcohol afforded **I.166** in a very good overall yield and also on large scale. It is important to mention that without activation of the ketone functionality of **I.163** by the Lewis acid $LaCl_3$, the yield dropped significantly on larger scale.

Via the next three steps, the methoxy group was converted into the ethyl group. For this purpose, the methoxy group was first deprotected with BBr_3 and then converted to the triflate.[133] A final Negishi cross-coupling[79] of the triflate afforded **I.169** in 78% yield over three steps. The second quaternary center was then introduced by a two-step sequence of 1,2-addition of allylmagnesium bromide and subsequent oxy-Cope rearrangement[134] to obtain intermediate **I.170**, which was afterwards isomerized by Skrydstrup's protocol[135] to intermediate **I.171**.

For practical reasons, the synthesis of both intermediates **I.173** and **I.174** was shortened by removing the three steps to introduce the ethyl side chain. In our opinion, the reactivity of the cyclohexanone part of the molecule does not change significantly if the aromatic part is substituted by a methoxy group instead of the ethyl side chain. Therefore, we synthesized intermediate **I.174** (Scheme 40) in the same way as reported for **I.171** (*vide infra*).



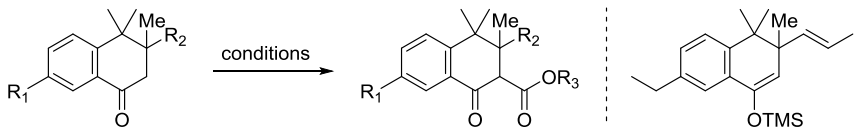
Scheme 39 Synthesis of intermediate **I.149** and the isomerized intermediate **I.171**.



Scheme 40 Synthesis of intermediate **I.173** and the isomerized intermediate **I.174**.

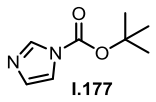
With these four intermediates in hands, the next steps toward the key steps were envisaged. For the Aldol condensation approach an ester at the α-position of the ketone was required. However, the α-acylation turned out to be challenging. The first idea was to introduce the ester by a direct acylation with dimethyl carbonate (DMC) (Table 16, entries 1–3). Since only starting material or decomposition could be observed, methyl chloroformate (entry 4) and the even more reactive Mander's reagent were used (entries 5–7), but again only starting material could be isolated. Interestingly, the use of LHMDS as base (entry 5) resulted in the formation of the TMS enol ether **I.176**, which was stable even during purification by column chromatography. With Boc-protected imidazole **I.177**[135] as acylating reagent (entry 8) only the starting material could be isolated.

Table 16 Screening of conditions for the direct α-acylation.

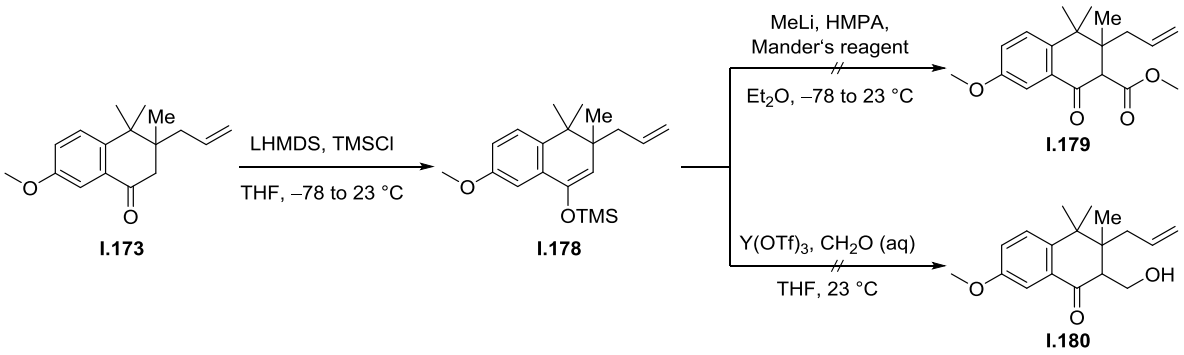


I.149: R_1 = Et, R_2 = allyl
I.171: R_1 = Et, R_2 = vinyl
I.173: R_1 = OMe, R_2 = allyl
I.174: R_1 = OMe, R_2 = vinyl

entry	substrate	base	reagent	result
1	**I.174**	NaH	DMC	no reaction
2	**I.174**	NaH, KH	DMC	decomposition
3	**I.171**	NaH	DMC	no reaction
4	**I.171**	NaH	methyl chloroformate	no reaction

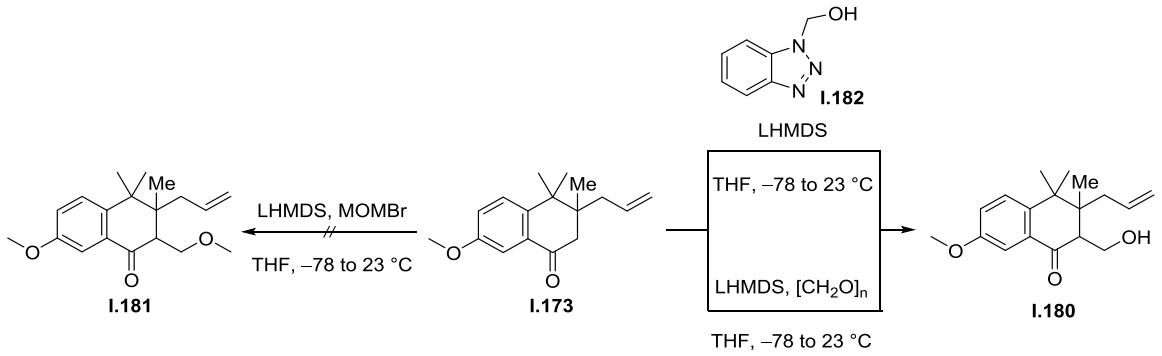
5	**I.171**	LHMDS	Mander's reagent	**I.176**
6	**I.171**	LDA	Mander's reagent	no reaction
7	**I.173**	LDA, HMPA	Mander's reagent	no reaction
8	**I.174**	NaH	 **I.177**	no reaction

However, the observation of the stable TMS enol ether **I.176** brought us to the idea to test a Mukajama Aldol reaction with **I.173** (Scheme 41), but again no reaction was observed. Due to all these negative results, we assumed that the bulkiness of the adjacent quaternary center prevents the attack at the electrophiles. We therefore started to focus on smaller electrophiles, such as formaldehyde, which could be oxidized afterwards. However, with aqueous formaldehyde and $Y(OTf)_3$, no reaction took place.[136]



Scheme 41 Attempted α-acylation via Mukajama Aldol reaction**.**

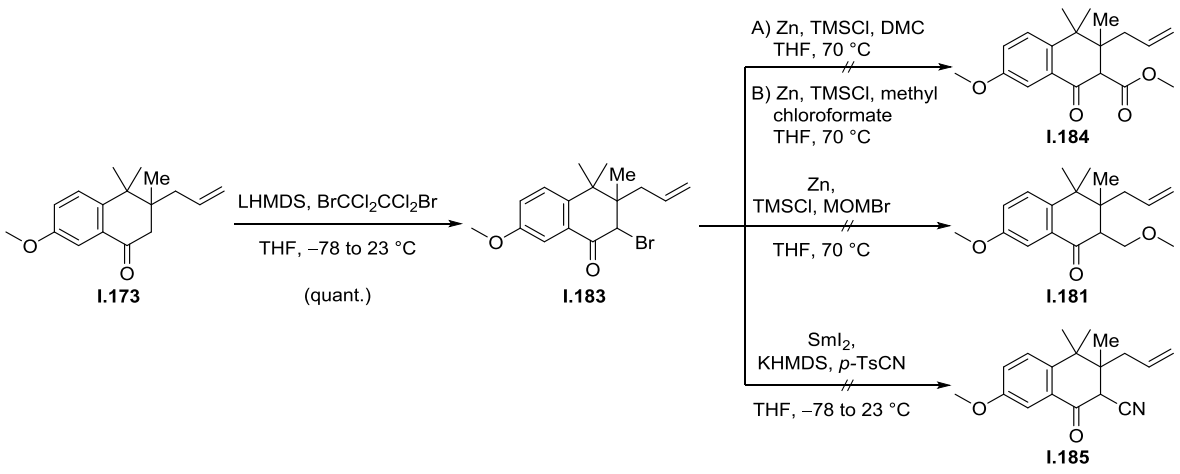
Thus, the next variant was to trap the deprotonated ketone **I.173** directly with the small electrophiles MOMBr and benzotriazole-1-methanol (**I.182**) (Scheme 42). Unfortunately, no reaction was observed. Another idea was to purge the reaction mixture with formaldehyde gas that was freshly prepared from paraformaldehyde. However, only **I.173** together with a complex mixture was obtained.



Scheme 42 Attempted formation of β-hydroxy ketones.

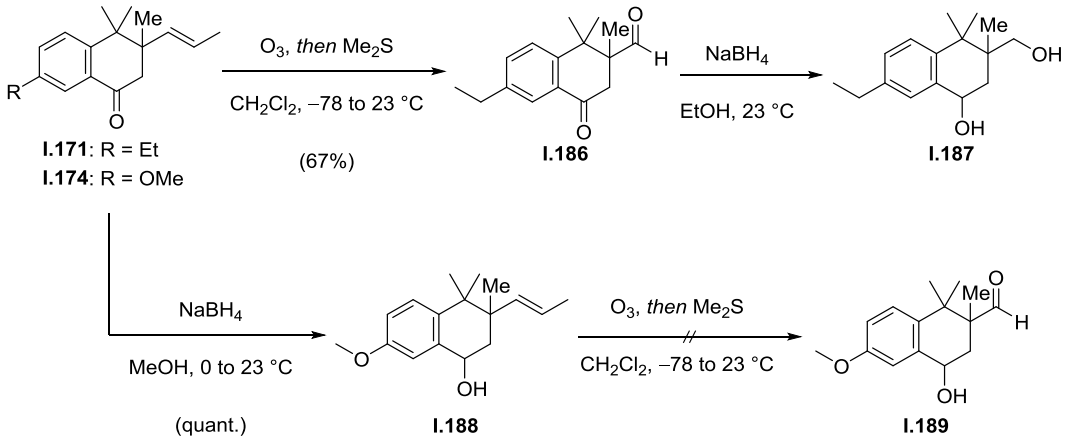
Our last approach to introduce either an ester or a synthetic equivalent thereof was to perform a Reformatsky reaction. From former quenching experiments it was known that halogen atoms could be introduced at the α-position of the ketone. Deprotonation with LHMDS and the use of 1,2-dibromotetrachloroethane as halogen source gave the brominated product **I.183** in quantitative yield (Scheme 43). With **I.183** in hands, several conditions for the alkylation were tested. For Zn, only the dehalogenated ketone **I.173** was isolated and the use of SmI_2[137] only led to a complex mixture.

At this point, we stopped our acylation efforts. The result of our attempts was that this α-position is apparently not reactive enough to attack electrophilic carbon atoms, independent of their sizes. However, it turned out that this position can easily be deprotonated and trapped with bulky halogen atoms in quantitative yield, which is in contrast to all the other observed results. Therefore, the lack of reactivity cannot be explained only by the sterics.



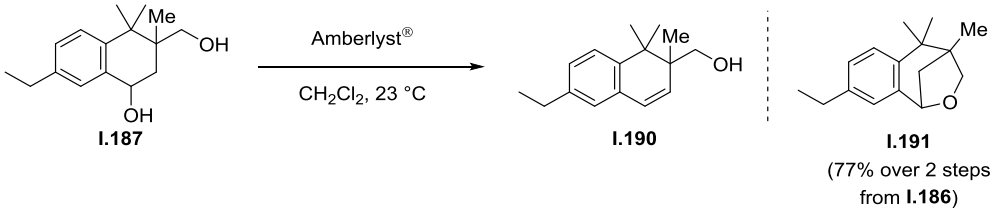
Scheme 43 Attempted Reformatsky reaction of **I.183**.

Therefore, we changed our strategy and focused on the [2+2]-cycloaddition approach. Starting from vinyl ketone **I.171**, the ozonolysis afforded ketoaldehyde **I.186** which was then reduced in a second step to diol **I.187** (Scheme 44). Unfortunately, we realized later that ketoaldehyde **I.186** was very sensitive toward further oxidation and even started to decompose during the work-up. Since we suspected the benzylic ketone to cause the problem, we reduced it to alcohol **I.188** and tested the ozonolysis again, but this time decomposition occurred.



Scheme 44 Ozonolysis of several vinyl substituted tetralins.

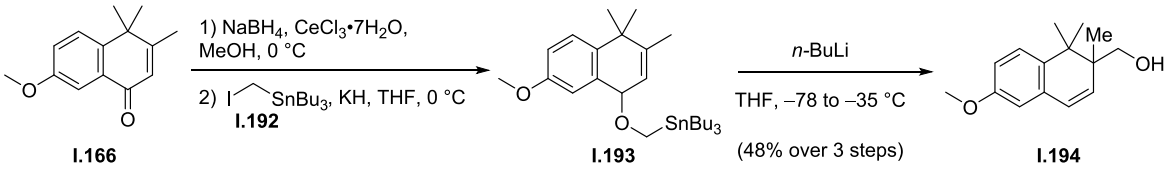
However, with a few milligram of diol **I.187** in hands, the elimination of the benzylic alcohol to the alkene was performed. In an attempt to dehydrate **I.187** using Amberlyst® at ambient temperature, we did not isolate the product **I.190**, but cyclic ether **I.191** in good yield (Scheme 45).



Scheme 45 Attempted elimination of the benzylic alcohol.

Since our initial attempt to generate **I.190** failed, we changed our strategy and went a few steps back in the synthesis. From our former route toward the intermediates with the two adjacent quaternary centers, we knew that we can overcome the steric repulsion of the *gem*-dimethylgroup by an intramolecular electrocyclization. Due to this, we envisaged to use a [2,3]-Wittig-Still rearrangement[138] to form the alkene moiety and the primary alcohol together in one step.

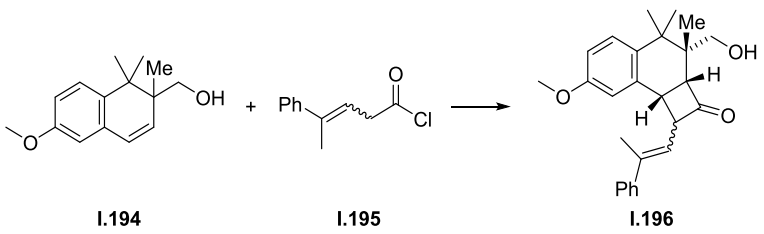
Starting from enone **I.166**, the first step was a Luche reduction to provide the very unstable benzylic, allylic alcohol (Scheme 46). To avoid elimination, the alcohol was immediately alkylated with tin reagent **I.192**[139] to afford **I.193**, the precursor for the [2,3]-rearrangement. This crude mixture was treated subsequently with *n*-BuLi and the desired product **I.194** was obtained in 48% yield over three steps. The common side-product of the Wittig-Still reaction, the [1,2] rearrangement product, was isolated in minor amounts and could be separated by flash column chromatography.



Scheme 46 [2,3]-Wittig-Still rearrangement.

With the substrate for the ketene [2+2] cycloaddition in hand, a variety of reaction conditions were screened in accordance to the literature (Table 17).[126] The two Lewis acids $AlMe_2Cl$ and $AlMe_3$ were tested as well as different concentrations of the reaction mixture in CH_2Cl_2, but only remaining starting material, traces of the ester of **I.194** and **I.195** and some kind of polymer were obtained. However, the acid chloride **I.195** was used in slight excess in contrast to the literature of Brown, but studies of Hugelshofer et al. showed that the cycloaddition also works with less ketene.[140] We thus guessed that our substrate was not reactive enough to undergo the cycloaddition and that the ketene therefore reacts with itself to form a dimer.

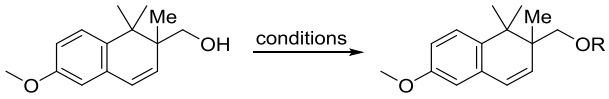
Table 17 Screening of conditions for the ketene-alkene [2+2] cycloaddition.



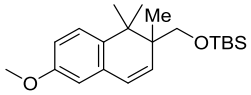
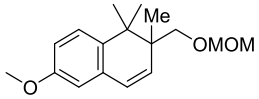
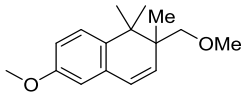
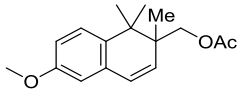
entry	conditions	result
1	DIPEA, $AlMe_2Cl$, CH_2Cl_2, −78 to 23 °C	**I.194** + ester
2	DIPEA, $AlMe_3$, CH_2Cl_2 (0.5 M), −78 to 23 °C	**I.194** + ester
3	DIPEA, $AlMe_3$, CH_2Cl_2 (1 M), −78 to 23 °C	**I.194** + ester

Hereupon, we changed to the more reactive ketene precursor trichloroacetyl chloride (**I.201**). With this, the cycloaddition product could be dehalogenated afterwards upon treatment with Zn and functionalized in another step.[141] However, we were not sure, if the reaction would tolerate the use of a Lewis acid to tether the ketene and decided to test the cycloaddition conditions without a Lewis acid. To avoid esterification with the acid chloride, the alcohol moiety was also protected with several protecting groups (Table 18).

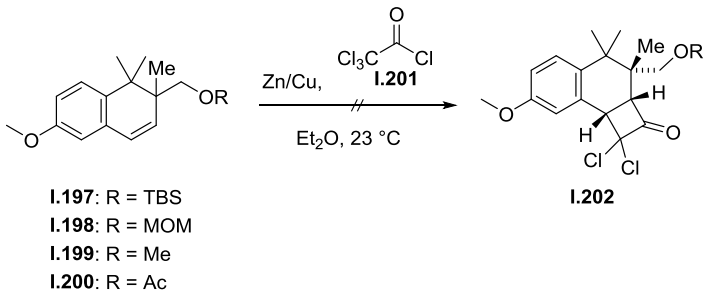
Table 18 Synthesis of protected alcohols.



I.194

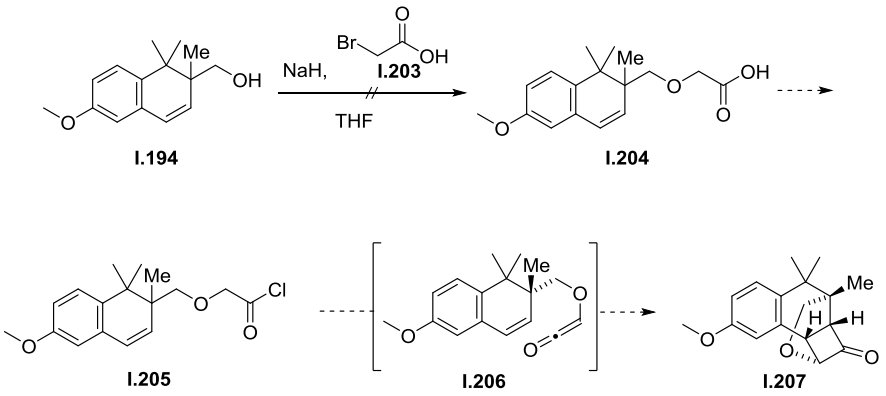
entry	conditions	result
1	TBSCl, im, DMF, 0 to 23 °C	 **I.197** (68%)
2	MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C	 **I.198** (94%)
3	MeI, NaH, DMF, 0 to 23 °C	 **I.199** (80%)
4	Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C	 **I.200** (86%)

The reactive species dichloroketene is generated in situ by dehalogenation of **I.201** with Zn/Cu couple and in order to avoid dimerization it is crucial to run the reaction under high dilution and to add the acid chloride very slowly to the zinc mixture.[142] With this in mind, the four substrates **I.197**–**I.200** were subjected to these conditions, but no conversion of the starting materials was observed (Scheme 47).



Scheme 47 Attempted [2+2] cycloaddition by in situ generated dichloroketene.

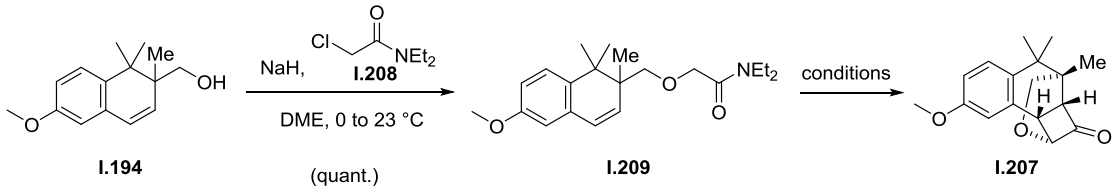
Since the previous results for the generation of the cyclobutanone were all not successful due to the low reactivity of the alkene substrate, we changed from the intermolecular [2+2] cycloaddition to an intramolecular version. This would have several advantages, since it is known that even very unreactive alkenes and ketenes react by an intramolecular cycloaddition to form complex polycyclic compounds. Furthermore, we would be able to control the stereoselectivity of the newly formed stereocenters. Our plan was thus to synthesize (alkenyloxy)acetic acid **I.204** and generate then the corresponding acid chloride **I.205** (Scheme 48). Heating this with Et_3N would lead to ketene **I.206**, which should cyclize to the tetracyclic product **I.207**. The regioselectivity of the addition was proposed to be as depicted for **I.207**, because the partial positive charge of the transition state would be stabilized at the benzylic position.[143] Unfortunately, the synthesis of acetic acid **I.204** was not possible and only starting material was observed.



Scheme 48 Envisaged synthesis of the tetracyclic compound **I.207**.

For this reason, we modified the reaction again, to synthesize an alkoxyamide with which an intramolecular keteniminium [2+2] cycloaddition could take place. An advantage of this modification would be the positive charge of the keteniminium which makes the reagent more electrophilic than ketenes and in addition prevents dimerization.[144] The amide precursor **I.209** for the key step was prepared in quantitative yield by nucleophilic substitution with 2-chloroacetamide **I.208** (Table 19). Thereupon, several conditions for the cycloaddition were screened. Different equivalents of Tf_2O and collidine as well as various reaction temperatures and times were tested. Another point was to vary the way how the Tf_2O and the collidine were added to the reaction mixture. The best result with 70% yield of the envisaged tetracyclic product **I.207** was obtained when Tf_2O and collidine were added at 23 °C to the substrate in 1,2-dichloroethane and the mixture was then heated to 80 °C (entry 10).

Table 19 Screening of conditions for the thermal intramolecular alkoxyketeniminium [2+2] cycloaddition.

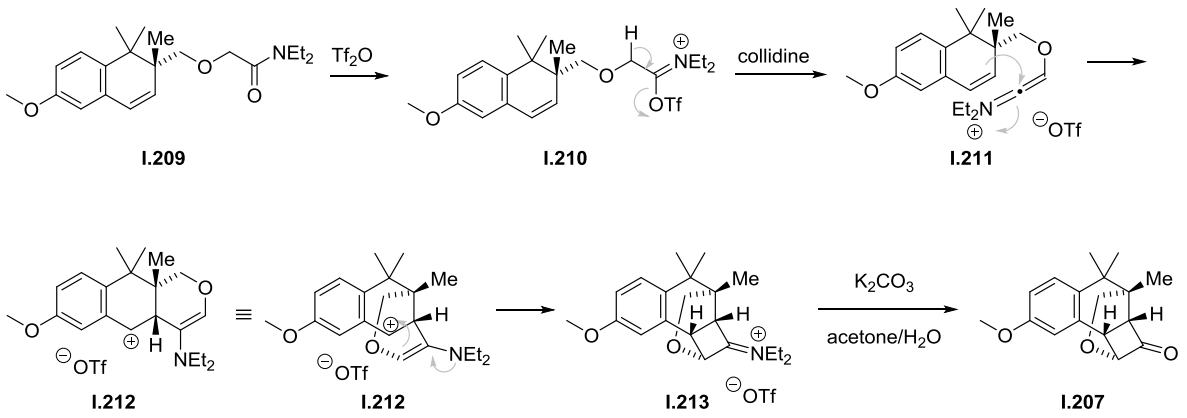


entry	conditions	comment	result
1	Tf_2O (1.1 equiv), collidine (1.2 equiv), DCE, 23 °C, 4 h, *then* CCl_4/H_2O, 100 °C	addition of Tf_2O over 45 min	no reaction
2	Tf_2O (1.1 equiv), collidine (1.2 equiv), DCE, 80 °C, 24 h, *then* acetone/H_2O, 80 °C	addition of Tf_2O over 5 h	**I.207** (36%)
3	Tf_2O (1.1 equiv), collidine (1.2 equiv), DCE, 80 °C, 24 h, *then* acetone/H_2O, 80 °C	addition of Tf_2O in one portion	**I.207** (traces) + decomposition
4	Tf_2O (5.0 equiv), collidine (5.0 equiv), DCE, 80 °C, 2.5 h, *then* acetone/H_2O, 80 °C	addition of Tf_2O in one portion	**I.207** (40%)
5	Tf_2O (3.0 equiv), collidine (3.0 equiv), DCE, 65 °C, 1 h, *then* acetone/H_2O, 65 °C	addition of Tf_2O in one portion	decomposition
6	Tf_2O (2.5 equiv), collidine (2.5 equiv), DCE,	addition of Tf_2O in	**I.207** (36%)

	55 °C, 30 min, *then* acetone/H_2O, 55 °C	one portion	
7	Tf_2O (2.5 equiv), collidine (2.5 equiv), DCE, 60 °C, 1 h, *then* acetone/H_2O, 60 °C	addition of Tf_2O in one portion	**I.207** (25%)
8	Tf_2O (5.0 equiv), collidine (5.0 equiv), DCE, 60 °C, 2.5 h, *then* acetone/H_2O, 60 °C	addition of Tf_2O in one portion	**I.207** (traces)
9[a]	Tf_2O (5.0 equiv), collidine (5.0 equiv), DCE, 80 °C, 2 h, *then* acetone/H_2O, 80 °C	addition of Tf_2O in one portion	**I.207** (55%)
10[b]	Tf_2O (5.0 equiv), collidine (5.0 equiv), DCE, 80 °C, 2 h, *then* acetone/H_2O, 80 °C	addition of Tf_2O in one portion	**I.207** (70%)

[a] the reaction was performed at 0.0868 mmol scale; [b] the reaction was performed at 0.174 mmol scale.

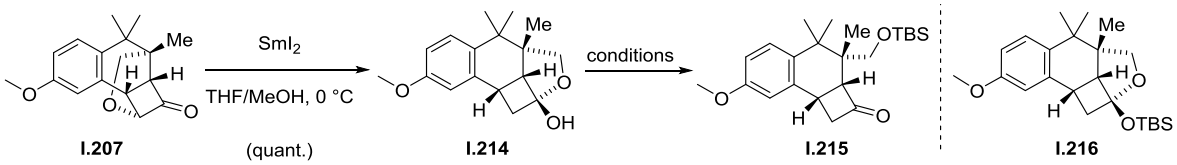
The mechanism of this thermal intramolecular alkoxyketeniminium [2+2] cycloaddition is depicted in Scheme 49. In the first step, the triflated cation **I.210** is formed, of which triflic acid is subsequently eliminated to form the keteniminium salt **I.211**. This ketene derivative is attacked by the benzylic alkene, resulting in the formation of a benzylic carbocation **I.212** which is subsequently trapped by the addition of enamine, forming the cyclic iminium ion **I.213**. The last step is the hydrolysis of the iminium toward ketone **I.207**. Mechanistic studies of Ghosez in 1983 showed that the reaction proceeds stepwise through a cationic intermediate and not concerted.[145] However, more recent studies discus also a concerted but highly asynchronous cycloaddition. The two mechanisms could also compete and depend on the nature of both the alkene and the ketene.[146]



Scheme 49 Proposed mechanism of the keteniminium [2+2]-cycloaddition.

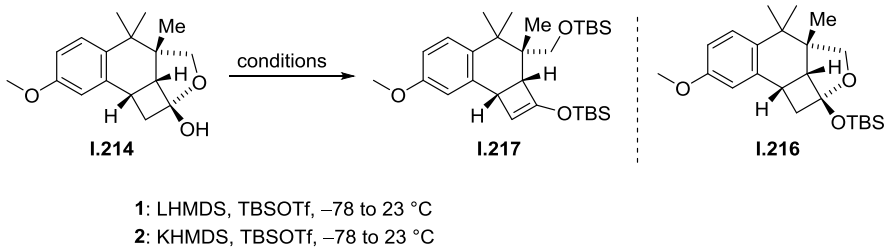
After the successful synthesis of tetracycle **I.207**, the ensuing step was to open up the cyclic ether. Therefore, **I.207** was treated with SmI_2,[147] but hemiketal **I.214** was obtained instead of the alcohol (Table 20). Therefore, the next aim was to open hemiketal **I.214** and trap the primary alcohol to prevent the ring closure. The fist idea was to use basic conditions in combination with a TBS silyl ether. The screened conditions for this transformation are depicted in Table 20, but although various bases, solvents and temperatures were tested, either starting material **I.214** or the protected tertiary alcohol **I.216** was isolated. The observation of the latter in quite high yields was surprising, since the protection of the tertiary alcohol should not be favored at all. However, this result gave us a first hint that the conformation of the hemiketal is way more preferred than its corresponding open form.

Table 20 Screening of conditions for the opening of hemiketal **I.214**.



entry	conditions	result
1	TBSCl, imidazole, DMF, 0 to 23 °C	no reaction
2	TBSOTf, Et_3N, CH_2Cl_2, −78 to −35 °C	81% **I.216**
3	TBSCl, imidazole, DMAP, DMF, 0 to 23 °C	no reaction
4	TBSCl, *t*-BuOK, THF, −78 to 23 °C	**I.216**
5	TBSCl, Et_3N, THF, 70 °C	no reaction

Since the screening of Table 20 with relatively mild bases was unsuccessful, the attention was turned to harsher conditions (Scheme 50). The intention this time was not only to protect the primary alcohol, but also form the silyl enol ether of the ketone. As soon as the ketone would be protected, the formation of the hemiketal is prohibited and the primary alcohol could be protected by the excess of reagents. However, the silyl ether of tertiary alcohol **I.216** was again the only observed product.

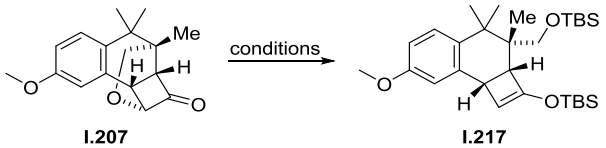


Scheme 50 Conditions for the formation of **I.217**.

A reason for the observations of Table 20 and Scheme 50 might be that, due to the very strained, bowl shaped structure of **I.214**, the primary alcohol points directly to the ketone and therefore the equilibrium between the hemiketal and its open form is almost completely on the side of the hemiketal. Another factor might be that the primary alcohol is neopentylic and therefore sterically quite hindered.

To overcome at least the problem with the equilibrium of the hemiketal, the idea was to prevent its formation during the cleavage of cyclic ether **I.207** (Table 21). Therefore, an excess of a SmI_2/HMPA complex was used to generate both the alkoxide and the enolate at the same time and trap both as silyl ether directly. Unfortunately, just starting material or a complex mixture was isolated (entries 1 and 2). A complex mixture was also obtained with just SmI_2, followed by addition of TBSOTf (entry 3).

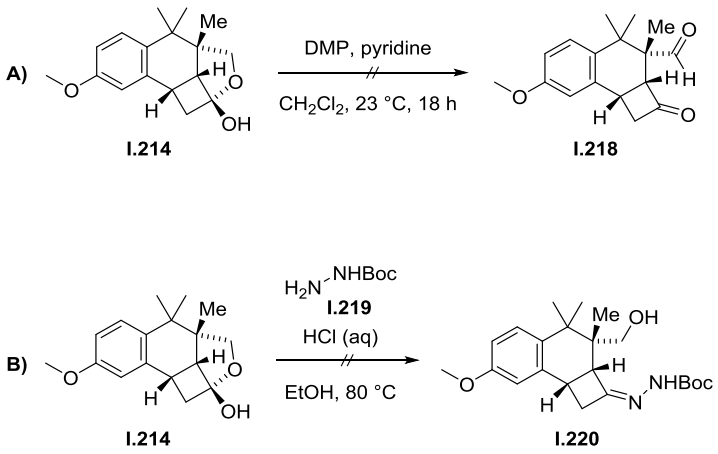
Table 21 Screening of conditions for the ring opening and twofold protection of **I.207**.



entry	conditions	result
1	SmI_2 (2.5 equiv), HMPA (5.0 equiv), TBSOTf, THF, 23 °C	no reaction
2	SmI_2 (15 equiv), HMPA (105 equiv), TBSOTf, THF, 23 °C	complex mixture
3	SmI_2, TBSOTf, THF, 23 °C	complex mixture

Since all the attempts to avoid the formation of the hemiketal or drive its equilibrium to the open form by trapping the primary alcohol failed - maybe also due to the sterical hindrance of the neopentylic position - a different kind of protecting group was needed. The envisaged key

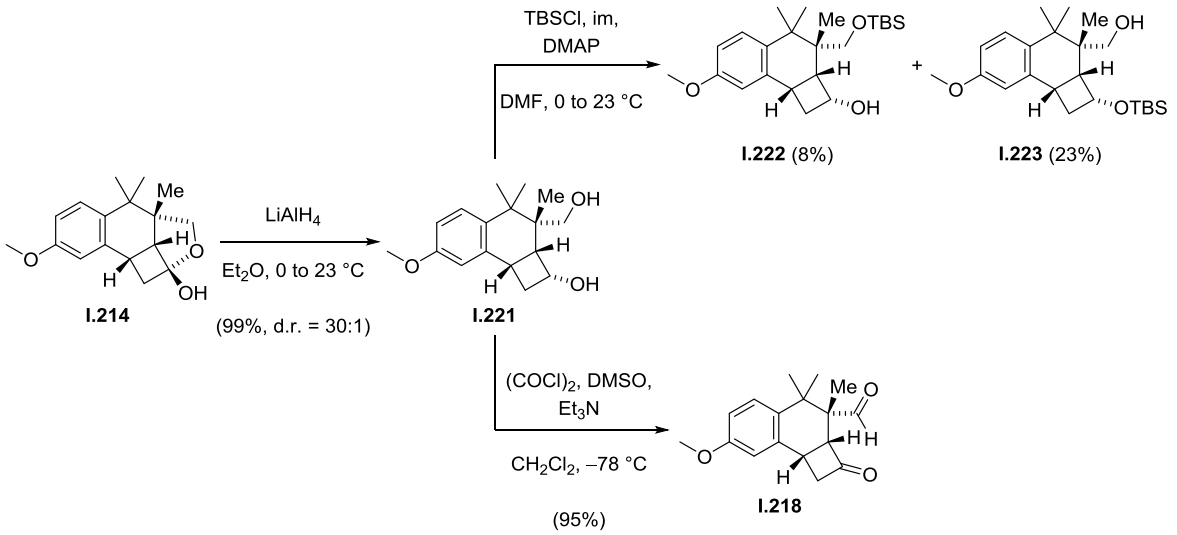
step to build the cycloheptenone affords an aldehyde group at exactly the position of the primary alcohol. An aldehyde would be on the one hand small enough for this congested position and on the other hand would reduce the number of steps by two. Thus, the hemiketal **I.214** was exposed to oxidative conditions but no reaction at all could be observed (Scheme 51A). Another option was to treat hemiketal **I.214** with *t*-butyl carbazate (**I.219**) under acidic conditions to obtain hydrazone **I.220**, but no conversion of the starting material was observed (Scheme 51B).[148]



Scheme 51 Attempted opening of hemiketal **I.214**.

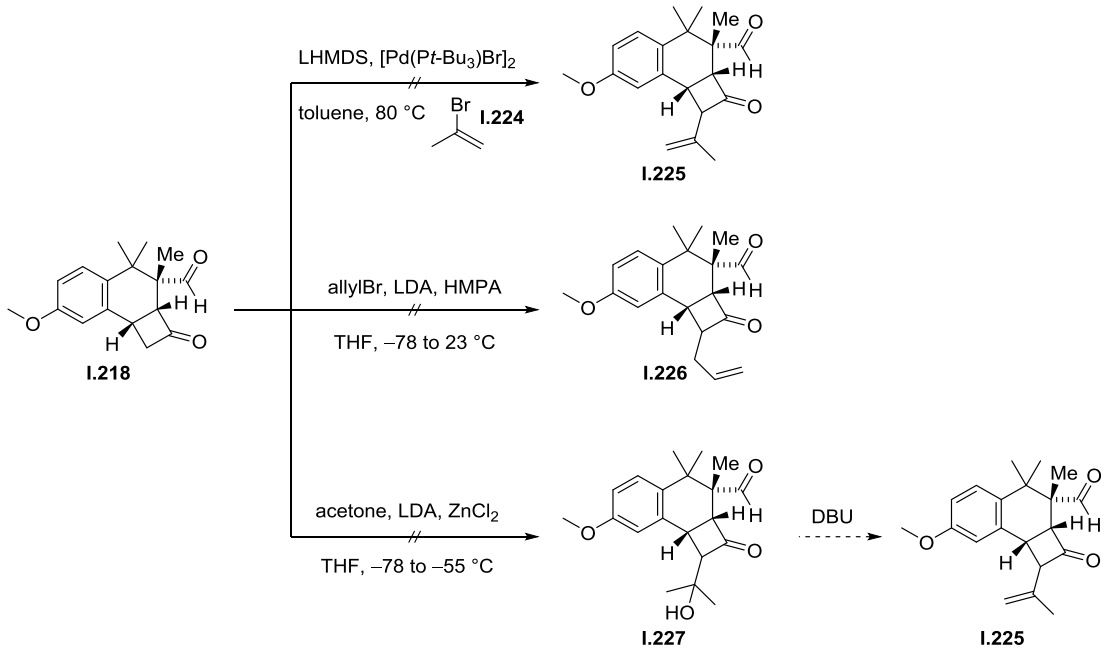
Although this attempt was unsuccessful, a similar approach came to our mind. Instead of subjecting **I.214** to oxidative conditions, it was treated with $LiAlH_4$ and in fact, diol **I.221** was afforded in very good yield and diastereoselectivity (Scheme 52). The proximate reaction was the selective protection of the primary alcohol **I.222**, but the main product was the silylated secondary alcohol **I.223**, presumably due to the sterically hindered neopentylic position.

To avoid this problem and since ketoaldehyde **I.218** is needed anyway, diol **I.221** was oxidized under Swern conditions to give **I.218** in very good yield.



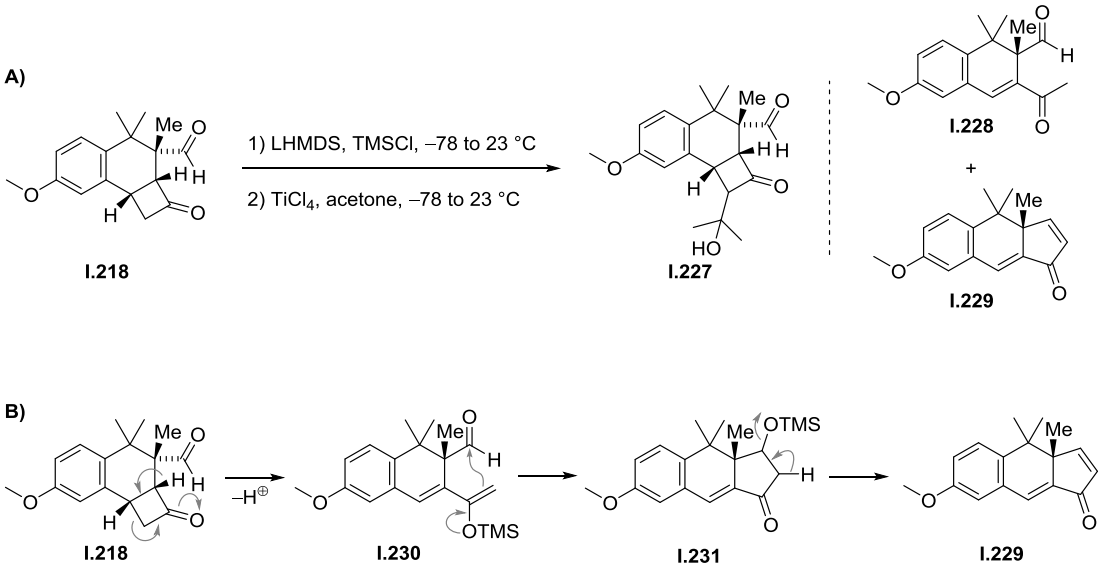
Scheme 52 Reduction of hemiketal **I.214** to diol **I.221** and further transformations.

With dicarbonyl **I.218** in hands, several attempts to alkylate the secondary α-position of the ketone were performed (Scheme 53). First of all, a Pd-catalyzed α-vinylation by a procedure of Huang et al. was tested,[149] but only decomposition was observed. Since alkylations with vinyl groups are often difficult the next idea was to use allyl bromide as electrophile. However, the product was again not obtained. An aldol addition with acetone and subsequent elimination of the tertiary alcohol with DBU was another idea to introduce a vinyl group, which contains a methyl group at the C2-position, but the envisioned product could not be isolated.[150]



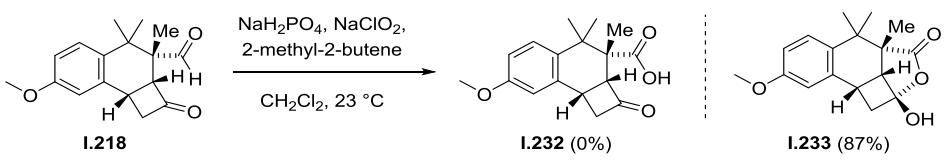
Scheme 53 Attempted alkylation and aldol addition of ketone **I.218**.

Since the direct alkylation and aldol condensation respectively were not successful, a Mukaiyama aldol reaction was envisaged. The product after the first step, the generation of the TMS enol ether, was used directly in the next step without any purification (Scheme 54A). $TiCl_4$ and acetone were added,[151,152,153] but the aldol condensation product **I.227** was not obtained. Instead, ketoaldehyde **I.228** and its aldol condensation product **I.229** were isolated. A possible explanation could be that the deprotonation with LHMDS occurred at the tertiary α-position of **I.218** instead of the more accessible secondary one (Scheme 54B). Therefore, the cyclobutanone ring was opened and the TMS enolate of ketone **I.230** was formed, which partially underwent an intramolecular aldol condensation to give **I.229**.



Scheme 54 A) Attempted Mukajama aldol addition. B) Proposed mechanism of the formation of **I.228** and **I.229**.

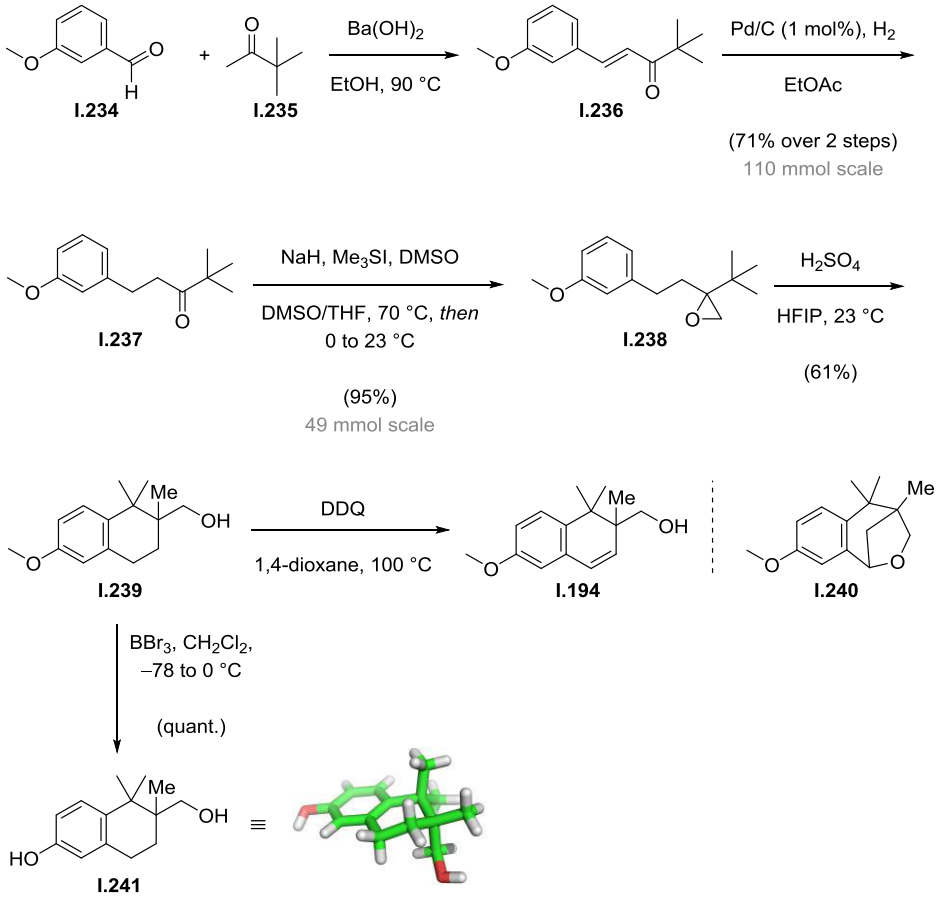
Our last idea was to oxidize the aldehyde moiety of **I.218** to the carboxylic acid, to ease the differentiation between the two carbonyl groups. Thus, aldehyde **I.218** was treated with classical Pinnick oxidation conditions. However, the so formed carboxylic acid attacked the cyclobutanone and formed again a hemiketal.



Scheme 55 Pinnick oxidation of aldehyde **I.218**.

2.2.2 Optimized Synthesis of the Precursor for the Intramolecular Alkoxyketeniminium [2+2] Cycloaddition‡

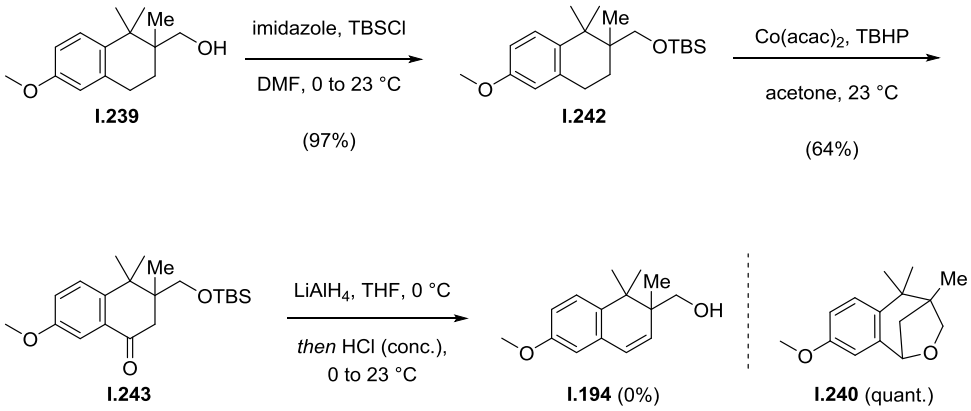
Since a major problem with the above reported synthesis was the permanent lack of material due to too many steps toward the key step, it was decided to develop in parallel a new synthetic route for alcohol **I.194**. This new route started with a $Ba(OH)_2$ catalyzed aldol condensation of *m*-anisaldehyde (**I.234**) and pinacolone (**I.235**).[154] Subsequent hydrogenation of the obtained enone provided ketone **I.237** in good yield (71%, >13 g) over two steps (Scheme 56). Corey-Chaykovsky epoxidation afforded epoxide **I.238** after the next step in very good yield (95%, >10 g).[155] Screening of conditions for the Friedel-Crafts alkylation revealed that the reaction afforded the best yield and regioselectivity in HFIP with a catalytic amount of concentrated H_2SO_4.[156] Small amounts of the *ortho*-Friedel-Crafts product could be isolated as well. Unfortunately, the benzylic oxidation of **I.239** with DDQ to the alkene **I.194** did not afford the envisioned product, but cyclic ether **I.240**, which was also the product of a previous reaction (compare Scheme 45). A crystal structure of **I.241** was obtained by deprotection of the Friedel-Crafts adduct.



Scheme 56 Synthesis of alcohol **I.239** and subsequent DDQ oxidation.

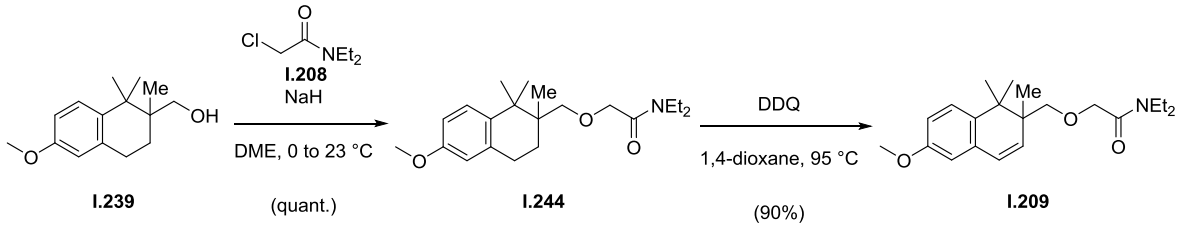
‡ The experiments of of Chapter 2.2.2 were performed in cooperation with Matthias Schmid.

The next idea was therefore to protect the primary alcohol **I.239** as TBS ether **I.242** and oxidize the benzylic position to ketone **I.243** (Scheme 57).[131,157] Subsequent reduction with $LiAlH_4$ and in situ deprotection of the silyl protecting group afforded however not alcohol **I.194**, but again cyclic ether **I.240** in quantitative yield.



Scheme 57 Benzylic oxidation of **I.242** and attempted elimination toward **I.194**.

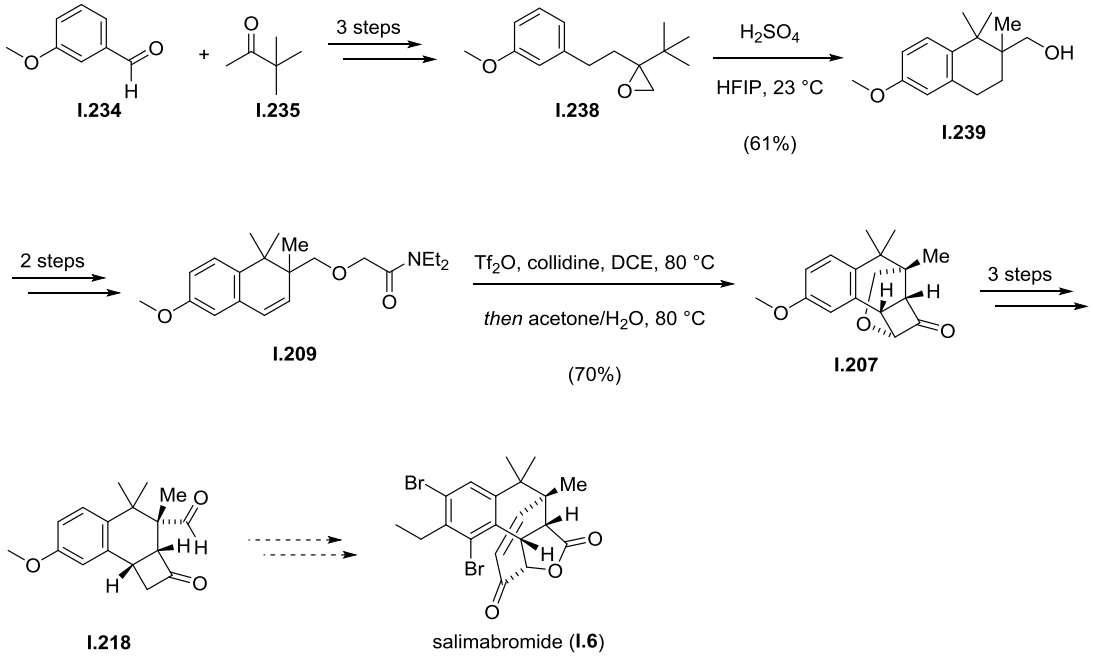
We then had another idea, which would also avoid a protection/deprotection sequence. The amide mojety for the keteniminium cyclization could also be used as "protecting group" for the benzylic oxidation to the alkene (Scheme 58). The first step, the formation of amide **I.244**, occurred in quantitative yield. Subsequent oxidation provided then alkene **I.209** in very good yield after some screening for the best conditions. It turned out that the reaction worked best in 1,4-dioxane with six equivalents of DDQ. In toluene or with less or more DDQ, either decomposition or incomplete conversion was observed.



Scheme 58 Synthesis of precursor **I.209** for the [2+2] cycloaddition.

3 Conclusion and Outlook

In summary, several approaches toward the total synthesis of the natural product salimabromide (**I.6**) have been investigated in this thesis. The epoxide **I.238** was synthesized in three steps from the commercially available starting materials **I.234** and **I.235** (Scheme 59). Subsequent cascade reaction consisting of a 1,2-methyl migration followed by Friedel-Crafts alkylation afforded bicyclic primary alcohol **I.239** in good yield. Due to this elaborate reaction, two adjacent all carbon quaternary centers were set in a single step. The synthesis of alkoxyamide **I.209** subsequently proceeded in two steps and set the stage for the keystep. Intramolecular keteniminium [2+2] cycloaddition of alkoxyamide **I.209** provided the envisaged tetracyclic product in 55% yield. To the best of our knowledge, this is the most complex substrate where such a keteniminium cycloaddition has been successfully applied. Three ensuing steps gave dicarbonyl compound **I.218**, which proved to be difficult to further functionalize toward salimabromide (**I.6**). Future studies are directed at advancing late-stage ketoaldehyde **I.218**.

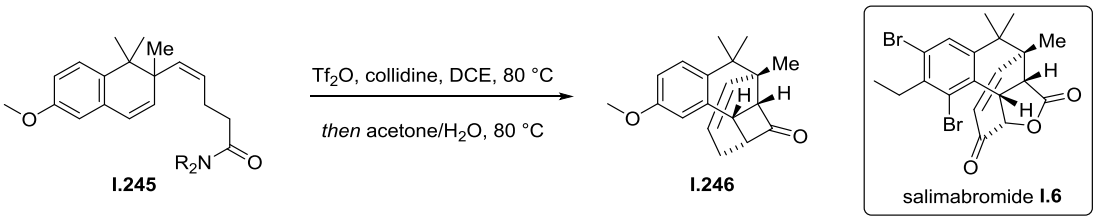


Scheme 59 Synthesis of an advanced intermediate for the synthesis of salimabromide (**I.6**).

To shorten the synthesis the use of elongated amide **I.245** will be investigated in the [2+2] cycloaddition instead of the alkoxyamide **I.209** (Scheme 60). This would have the advantage that

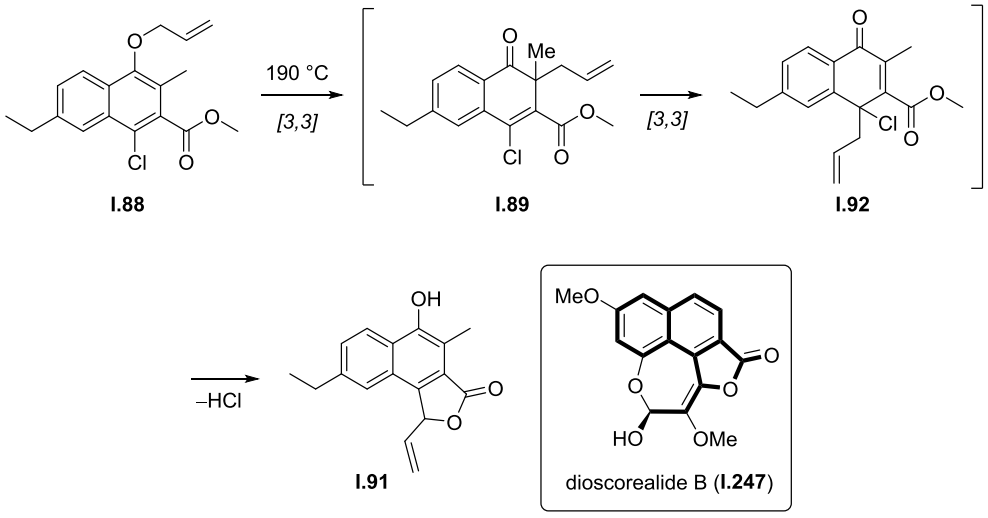
– following Baeyer-Villiger oxidation of the cyclobutanone - the thus formed seven-membered ring **I.255** would simply require an allylic oxidation to establish the tetracyclic core structure of salimabromide (**I.6**).

In further experiments, the substitution pattern of the aromatic portion of salimabromide (**I.6**) would be introduced. To avoid any additional sterical hindrance during the keteniminium [2+2] cycloaddition, bromination is planned to occur at a later stage of the synthesis.



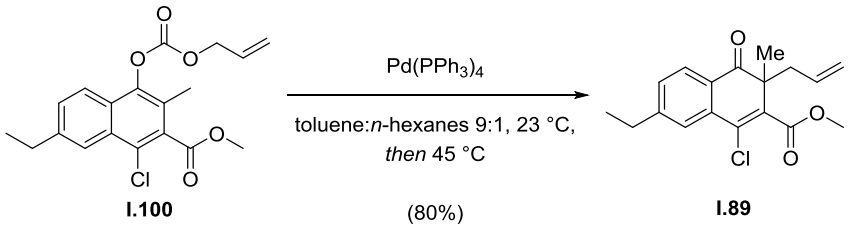
Scheme 60 New approach for the keteniminium [2+2] cycloaddition.

During these studies toward salimabromide (**I.6**), several new and interesting reactions were discovered, such as the cascade reaction of allyl naphthyl ether **I.88** that provided a tricyclic lactone (**I.91**) (Scheme 61). Further exploration of this reaction could provide rapid access to natural products with similar structural motif, such as dioscorealide B (**I.247**).



Scheme 61 Cascade reaction to yield tricyclic lactone **I.91**.

With the Pd-catalyzed intramolecular dearomatization of 1-naphthols another powerful transformation was investigated for a new substrate class. This reaction enabled the successful installation of an all carbon quaternary center at the C2-position of the former naphthol and was capable of proceeding on multi-gram scale (Scheme 62). To date, no such dearomatization by a Tsuji allylation is known. As such, it was further investigated in a separate project and is presented in Chapter II of this thesis.



Scheme 62 Successful dearomatization of a 1-naphthol under Tsuji conditions.

CHAPTER II

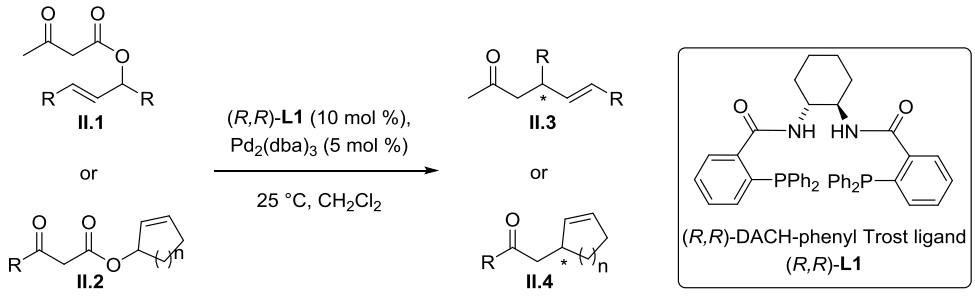
CATALYTIC ASYMMETRIC DEAROMATIZATION (CADA) REACTION

4 Introduction

4.1 Asymmetric Palladium Catalyzed Decarboxylative Allylations

The formation of new carbon-carbon bonds is one of the most fundamental reactions to create complex structures in organic chemistry. Several procedures to form C–C bonds have been developed in the past, however, the formation of quaternary centers and especially their asymmetric formation is still challenging. In recent years, significant improvement of the palladium catalyzed asymmetric allylic alkylation allows the generation of tertiary and quaternary centers in a highly asymmetric fashion. In general, there are two types of substrates for this reaction: allyl β-keto carboxylates (Scheme 63) and vinyl carbonates (Scheme 64).[158] However, in recent years even 2-naphthols turned out to be viable substrates, which undergo a dearomative allylation by generating selectively a quaternary center at the C1-position.

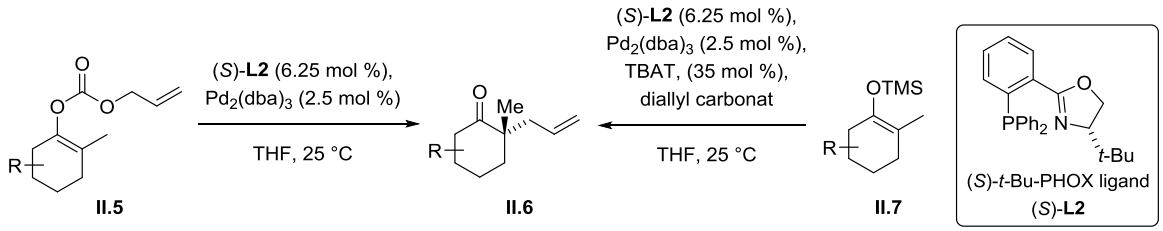
The first palladium catalyzed decarboxylative allylations were independently reported by Tsuji[89] and Saegusa[90] in 1980 within two days. However, the first asymmetric version of the so-called decarboxylative Tsuji allylation was reported over 20 years later in 2004 by Tunge and Burger (Scheme 63).[159] They were able to obtain yields up to 94% and *ee*'s ranging from 54% to 98%, using the (*R*,*R*)-DACH-phenyl Trost ligand ((*R*,*R*)-**L1**).



Scheme 63 First reported asymmetric Tsuji allylation.

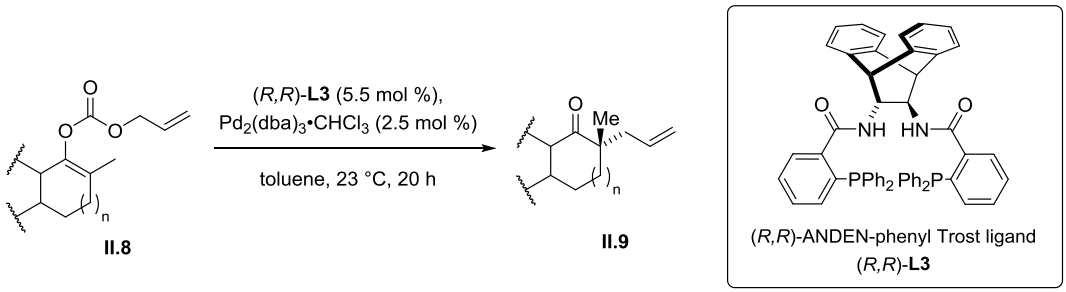
Only a few months later, Stoltz published a very similar methodology for an enantioselective Tsuji allylation of allyl enol carbonates **II.5** and silyl enol ethers **II.7** (Scheme 64).[98] In contrast to Tunge, who was able to control the stereocenter of the β-position, Stoltz and co-worker demonstrated the ability to control the stereochemistry at the α-position. A ligand screening showed that the PHOX ligands - and especially one with the *t*-butyl oxazoline - were able to improve the *ee*'s significantly. Using this methodology, Stoltz was able to construct all carbon

quaternary stereocenters both intra- and intermolecular in high yields (79–99%) and high *ee*'s (79–92%). The substrate scope covers a variety of 6 to 8 membered rings and 1-tetralones and also cyclic enol silanes, for which the use of tetrabutylammonium difluorotriphenylsilicate (TBAT) as initiator was essential.



Scheme 64 Asymmetric Tsuji allylation by Stoltz and co-workers.

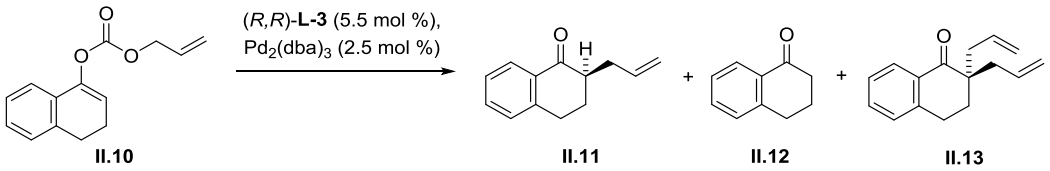
A few months later, Trost also published an enantioselective Tsuji allylation where the ANDEN-phenyl Trost ligand ((*R*,*R*)-**L3**) was used (Scheme 65).[96] The reaction was performed in toluene instead of tetrahydrofuran (THF) and the obtained yields (64–99%) and *ee*'s (76–100%) for the substrate scope, which even contains heterocycles, are similar to the ones of Stoltz. Notwithstanding the similarity to Stoltz methodology, Trost expanded this methodology to the synthesis of tertiary stereocenters and therefore simultaneously overcoming the issue of product racemisation and dialkylation.



Scheme 65 Asymmetric Tsuji allylation by Trost and co-workers.

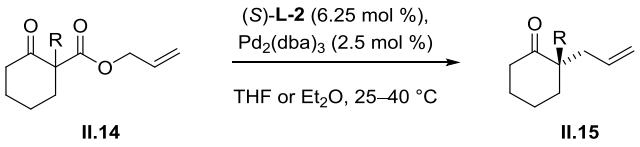
Employing the enol carbonate of 1-tetralone **II.10** as model substrate for a solvent screening gave astonishing results. In toluene and especially in THF substantial amounts of unalkylated and dialkylated side products **II.12** and **II.13** were observed (Scheme 66). Only when the reaction was conducted in 1,4-dioxane their formation was almost completely prevented. Trost

speculates that the absence of the side products results from the formation of solvent-caged contact ion pairs, which are predominantly generated in dioxane compared to other solvents. According to this assumption, the equilibrium of the enolate and the product will be minimized, if the alkylation reaction between the contact ion pairs is much faster than the diffusion rate of the ions or the product out of the solvent cages.[96]



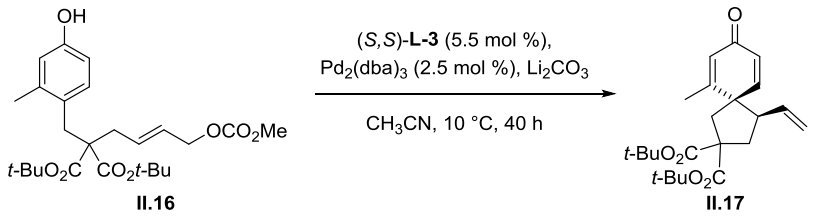
Scheme 66 General scheme for the asymmetric Tsuji allylation using 1-tetralones.

In 2005, Stoltz reported the first example of a very efficient deracemization of α-substituted β-ketoesters **II.14** by a decarboxylative Tsuji allylation (Scheme 67). In this work, Stoltz and co-workers explored an enantioconvergent reaction mechanism "in which the same catalyst is intimately involved in both the stereoablative (C–C bond-braking) and stereoselective (C–C bond-forming) steps."[160] By this, they expanded the scope to a variety of racemic β-ketoesters with α-quaternary centers, which could be transformed into their corresponding ketones in up to 99% yield and 92% *ee*.



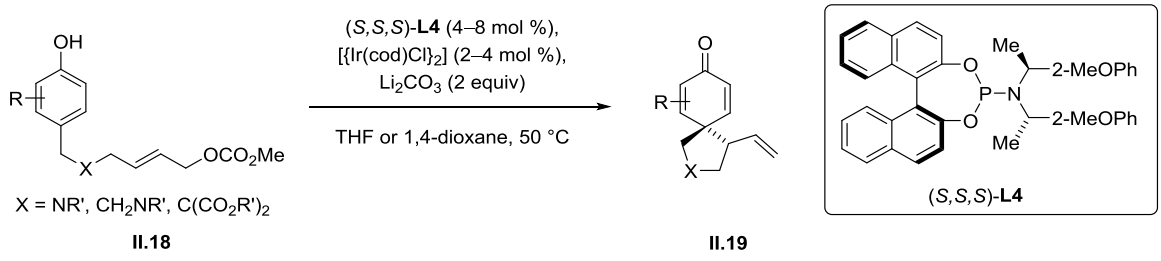
Scheme 67 Enantioconvergent deracemization of β-ketoesters.

Hamada published in 2010 the first Pd-catalyzed dearomative *ipso*-Friedel-Crafts allylic alkylation for the synthesis of spiro[4.5]cyclohexadienones (Scheme 68). Via this methodology, they were able to dearomatize phenol **II.16** and obtain spirocycle **II.17** as the major diastereomer in 80% yield (dr = 9.2:1) and 89% *ee*.[161] Further studies in 2012 confirmed that ligand (*R*,*R*)-**L3** gives the best results.[162]



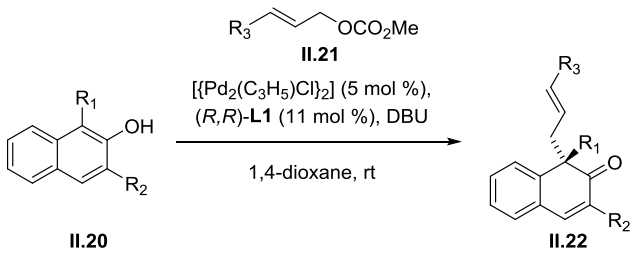
Scheme 68 Pd-catalyzed asymmetric *ipso*-Friedel-Crafts allylic alkylation.

In 2011, You published a quite similar reaction for the intramolecular asymmetric formation of spirocyclohexadienone derivatives **II.19** via the dearomatization of phenols. In contrast to Hamada, the reaction is Ir-catalyzed and the phosphoamidite ligand (*S,S,S*)-**L4** is used, which provides a wide scope of spirocycles in 60–95% yield and 85–97% *ee*. Again, the use of Li_2CO_3 was crucial for the reaction outcome.[163]



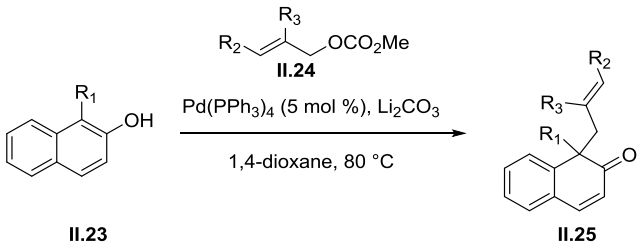
Scheme 69 Ir-catalyzed asymmetric *ipso*-Friedel-Crafts allylic alkylation.

Notwithstanding the complexity of the spirocyclic products by Hamada and You, the design of the phenolic starting materials for the intramolecular dearomatization prevents competing *O*- and *ortho*-alkylation. In 2013, You overcame this problem and reported the first Pd-catalyzed intermolecular asymmetric allylic dearomatization of 2-naphthols (**II.20**) (Scheme 70). Various carbonates (**II.21**) served as allyl sources in combination with a Pd(II)-catalyst and the Trost-ligand (*R,R*)-**L1**. This time, not Li_2CO_3 but DBU turned out to be the optimal base concerning enantioselectivity and chemoselectivity. The dearomatized products (**II.22**) with an all carbon quaternary center - generated in very good selectivity at the C1-position - were obtained in high yields and *ee*'s. However, the chemoselectivity of the allylation decreased considerably when the R^2-substituent was a hydrogen atom. Another drawback of this methodology is that the naphthols are used in excess with regards to the carbonates (2 equivalents vs. 1 equivalent).[72]



Scheme 70 Pd-catalyzed asymmetric intermolecular allylic dearomatization of 2-naphthols.

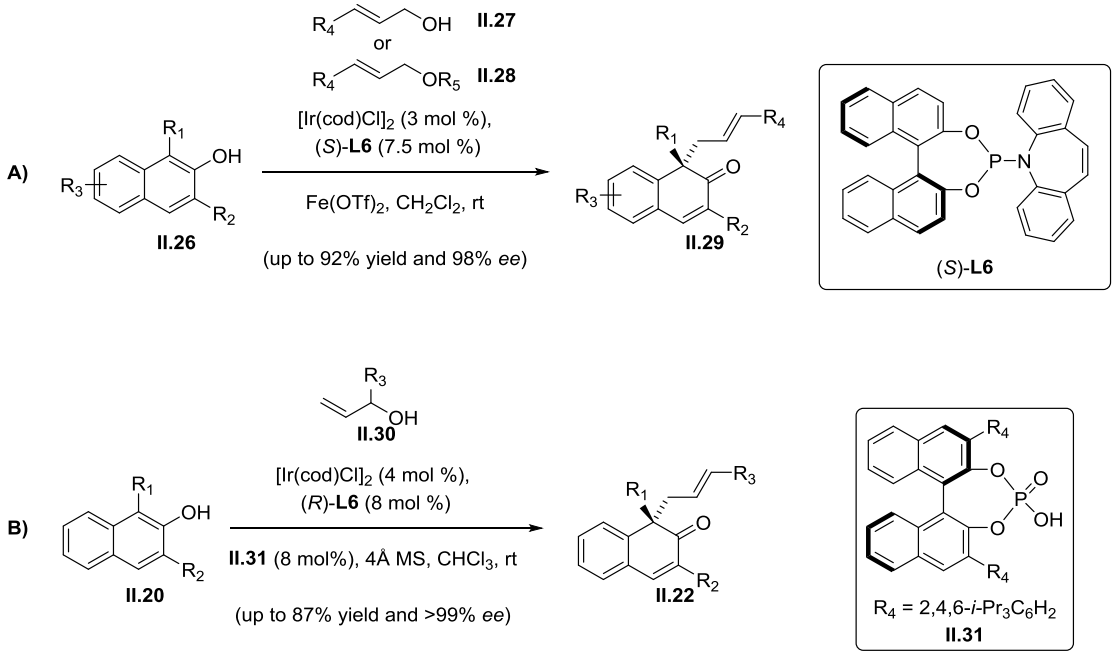
One year later You expanded his methodology and was able to obtain very good chemoselectivities for the dearomatization of 2-naphthols (**II.23**) even without a substituent at the C3-position. The best chemoselectivities were observed for ester or ketone substituents at the C1-position, maybe due to the electron withdrawing effect. However, the ratio of naphthol to carbonate is still 2 : 1. In contrast to the previously published methodology, the synthesis of the dearomatized substrates is racemic and at elevated temperatures. Interestingly, You also published a screening of chiral ligands, showing excellent conversion up to 90% but only providing *ee*'s of 10%.[164]



Scheme 71 Pd-catalyzed asymmetric intermolecular allylic dearomatization of 2-naphthols.

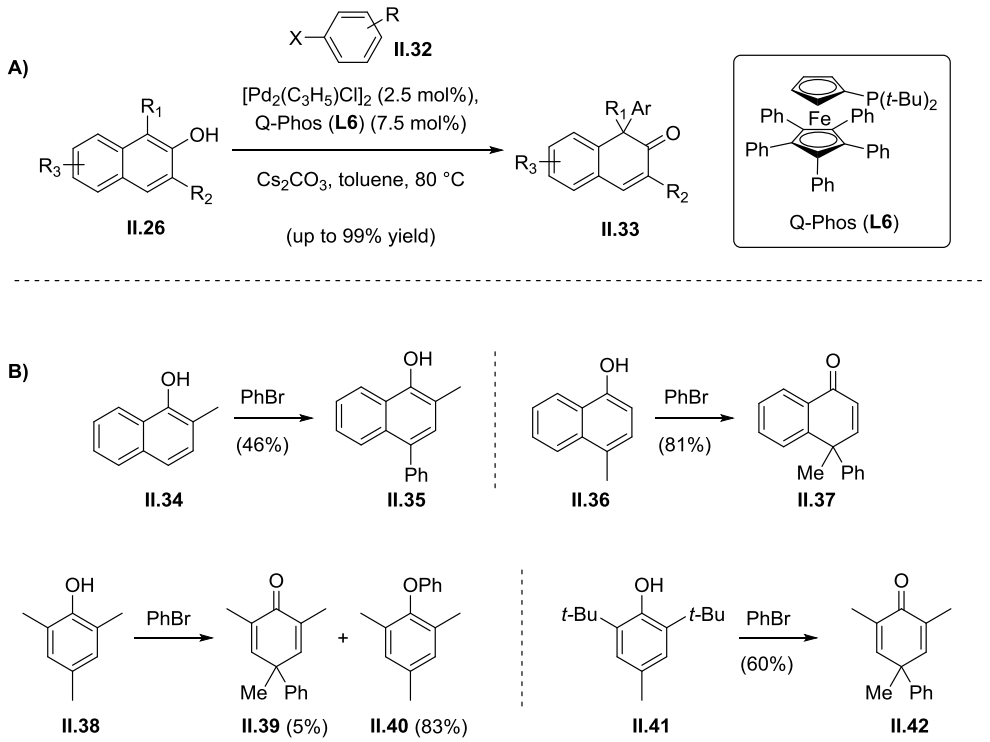
In 2017, You was able to overcome all the former problems of competing *O*-alkylation, low enantioselectivity and unpractical substrate to reagent ratio. An iridium-catalyst was employed, which allowed the use of the phosphoramidite ligand (*S*)-**L6** (Scheme 72A) and allylic alcohols (**II.27**) and ethers (**II.28**) were found to be suitable substrates instead of allyl carbonates. A beneficial feature of the use of allylic alcohols and ethers as substrates is the shorter synthesis and the reduction of the generated waste. However, a Lewis acid had to be added to activate the allylic alcohols and ethers. Screenings showed that Brønsted acids promote the reaction as well but with much lower efficiency.[165]

Just a month later, the Zhong group reported almost exactly the same methodology (Scheme 72B). With a chiral Ir/phosphoramidite complex they were able to dearomatize 2-naphthols (**II.20**) using allylic alcohols (**II.30**). The major difference between both reactions is that Zhong uses the chiral Brønsted acid **II.31** to activate the allylic alcohol.[166] Interestingly, the same Brønsted acid was also tested by You with mediocre success. Another notable difference is the used name for the dearomatization reaction: You refers to as catalytic asymmetric dearomatization (CADA) reaction and Zhong as asymmetric allylic dearomatization (AADA) reaction. To avoid confusion, the author of this thesis decided to just use the term CADA reaction.



Scheme 72 Catalytic asymmetric dearomatization reactions by You and Zhong.

Notwithstanding the results of You and Zhong, both use 2-naphthols for the allylic dearomatization which hinders or even prevents subsequent rearomatization via Cope rearrangement. The only publication that examined the intermolecular dearomatization of 1-naphthols and phenols by a similar methodology was published in 2016 by You. Herein the main topic is the arylative dearomatization of 2-naphthols (Scheme 73A). However, they also tried to expand the methodology to the dearomatization of 1-naphthol **II.34** by generating an all carbon quaternary center at the C2-position, but they only could obtain a C4-substituted dearomatized product **II.35** (Scheme 73B). The only dearomatization took place at a substituted C4-position (**II.37**). A very similar result was observed for phenols.[167]

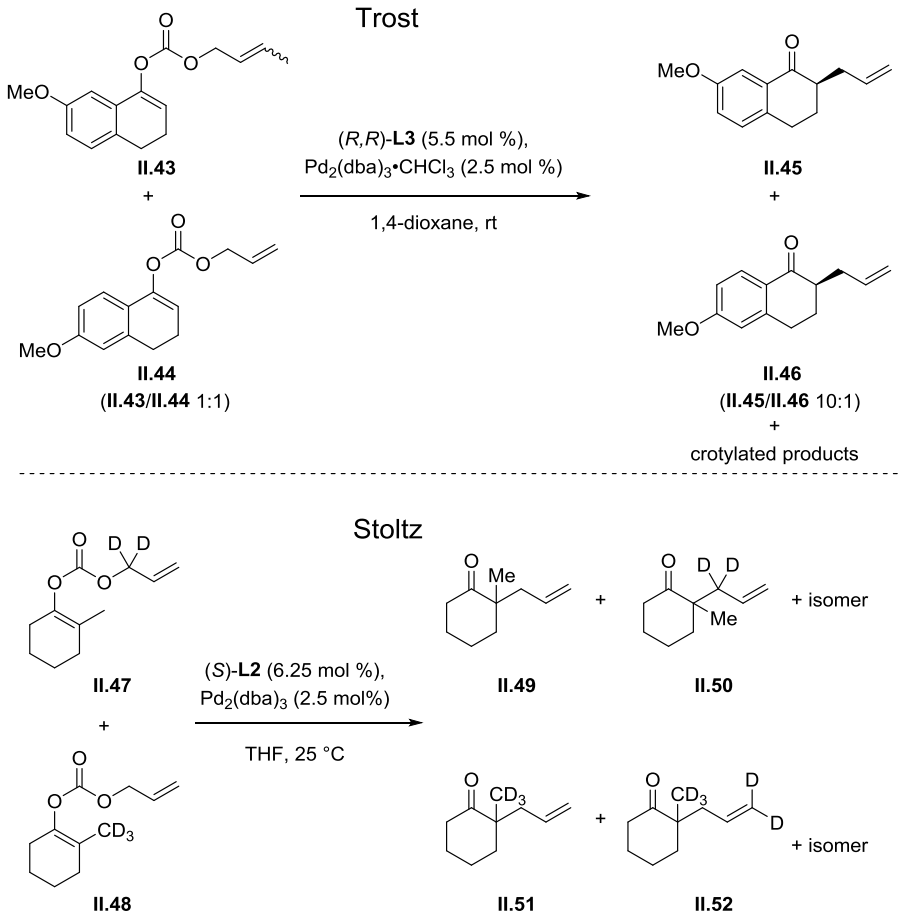


Scheme 73 Pd-catalyzed intermolecular arylative dearomatization.

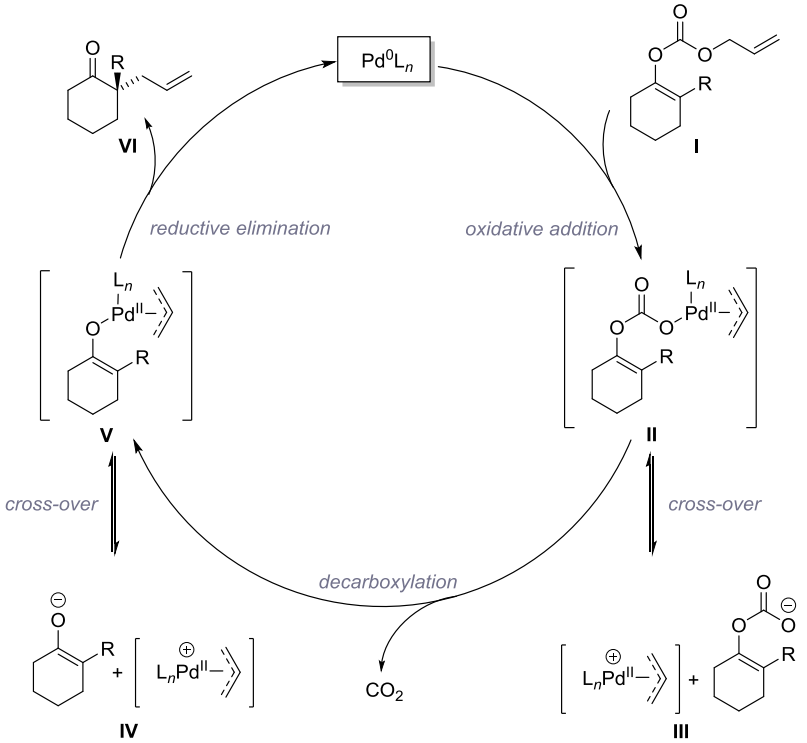
4.2 Mechanism of the Palladium-Catalyzed Asymmetric Alkylation

The first investigations toward the mechanism of the Pd-catalyzed Tsuji allylation were cross-over experiments performed by Stoltz[160,168] and Trost.[96] Interestingly, Trost's group observed only minimal cross-over between both allyl groups, yet Stoltz observed all possible cross-over products in a deuterium labelled experiment (Scheme 74). A possible explanation for the different results might be the influence of the ligands on the reaction mechanism.

Trost proposes that his catalytic system containing the bisphosphine ligand accelerates the alkylation reaction in such a way that it exceeds the rate of ion or product diffusion out of the solvent–cages formed in 1,4-dioxane. In contrast, Stoltz suggests a similar catalytic cycle as Saegusa in 1980,[90] which contains two stages for possible scrambling (Scheme 75). This cycle would also be consistent with the results that were observed with his catalytic system.

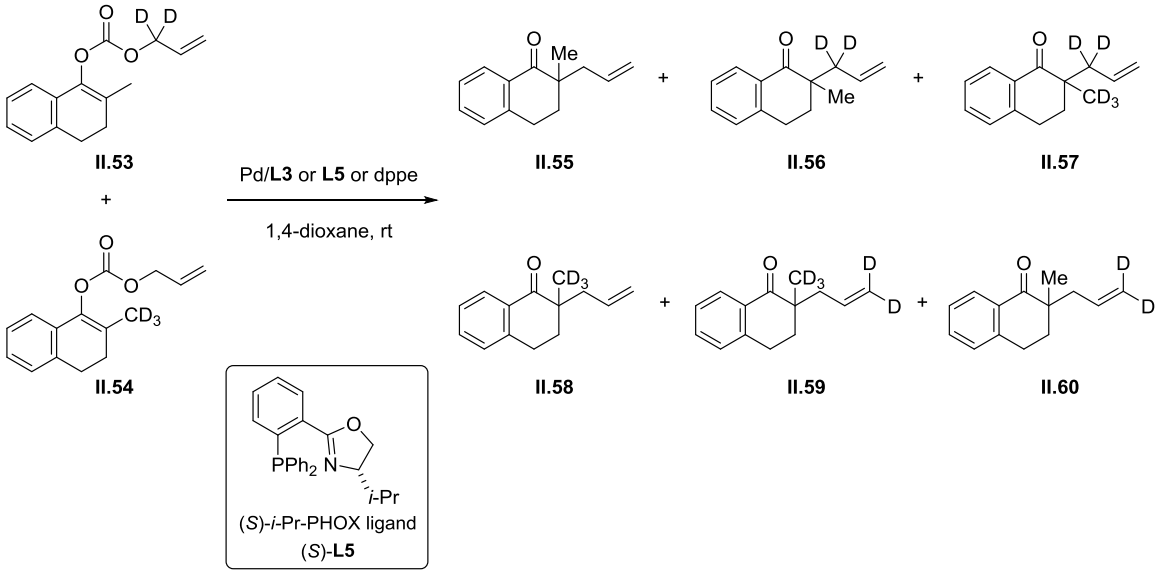


Scheme 74 Cross-over experiments performed by the groups of Trost and Stoltz.



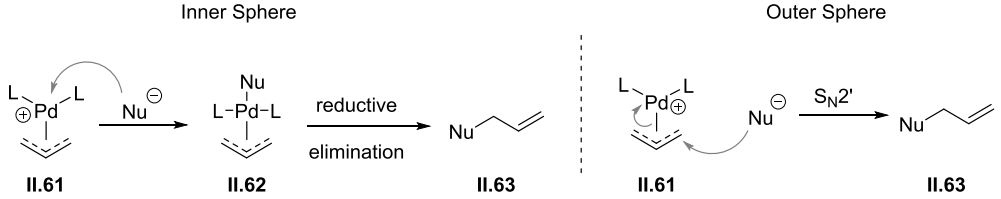
Scheme 75 Proposed catalytic cycle for the decarboxylative allylic alkylation by Stoltz and Saegusa.

A few years later, Trost published another experiment to investigate the scrambling during the Tsuji allylation. Trost used a very similar deuterated substrate as Stoltz in combination with the different ligands **L3**, **L5** and dppe (1,2-bis(diphenylphosphino)ethane) in 1,4-dioxane to rule out the influence of the substrate and the ligand (Scheme 76). Contrary to Trosts previous experiment, complete scrambling and thus formation of all six possible products was observed this time for all the tested ligands. Therefore he suggests now that the exchange of the ion-pairs is faster than the product generation.[169]



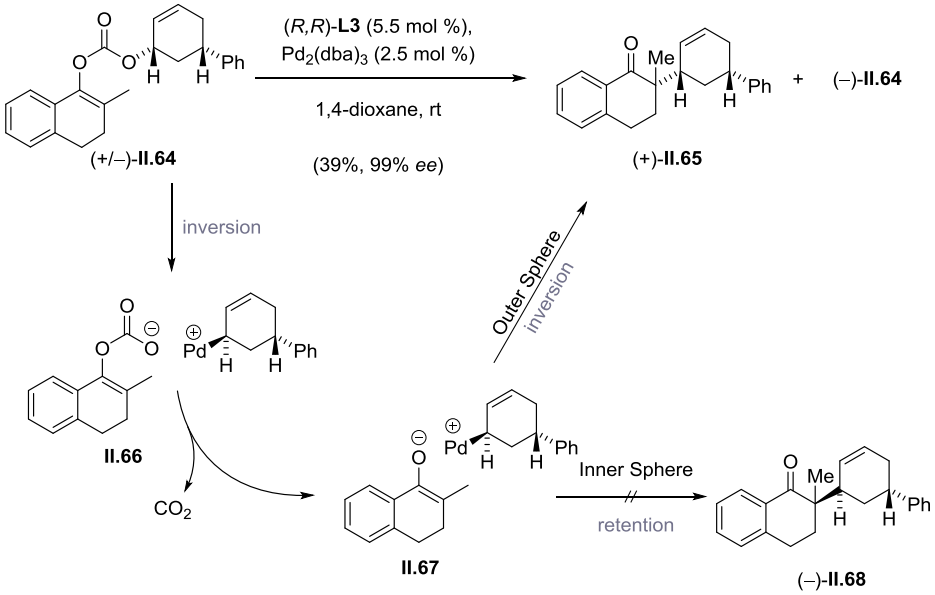
Scheme 76 Cross-over experiment of Trost from 2009.

Trost also discussed the two mechanistic pathways for the recombination of the enolate and the π-allylpalladium complex **II.61** (Scheme 77). In the inner sphere mechanism, the nucleophile coordinates first to the palladium, followed by a reductive elimination to form the product **II.63**. This mechanism is usually favored for "hard nucleophiles" with a p*K*a>20. The other possibility is the outer sphere mechanism where the nucleophile attacks directly the allyl moiety and substitutes the palladium in a S_N2' fashion. This pathway is arbitrarily favored by "soft nucleophiles" with a p*K*a<20.[169]



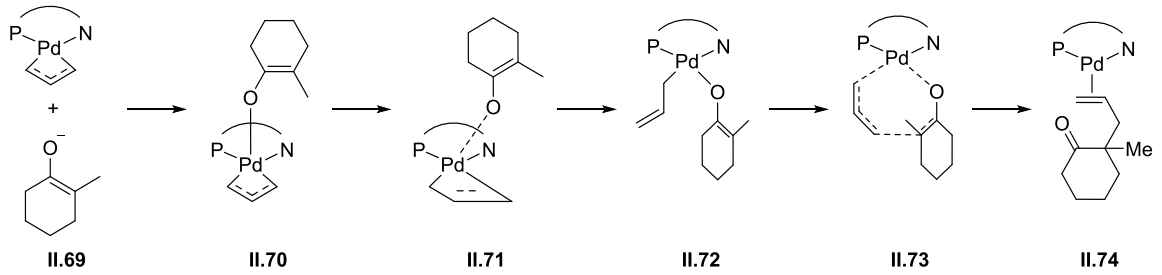
Scheme 77 Inner vs. outer sphere mechanism of the nucleophilic addition to the π-allylpalladium complex **II.61**.

To figure out which pathway is more likely for the decarboxylative Tsuji allylation, (±)-**II.64** was treated with the usual Trost conditions. The result was an almost perfect kinetic resolution since only one enantiomer of the racemate reacted selectively and the other one remained even after 12 h. Analysis of the configuration of the product **II.65** revealed the *cis* configuration and thus retention of configuration. Since ionisations of carbonates generally follow an *anti*-addition mechanism, the observation of the overall retention of configuration strongly indicates an "outer sphere" mechanism.[169]



Scheme 78 Palladium-catalyzed decarboxylative allylation of **II.64**.

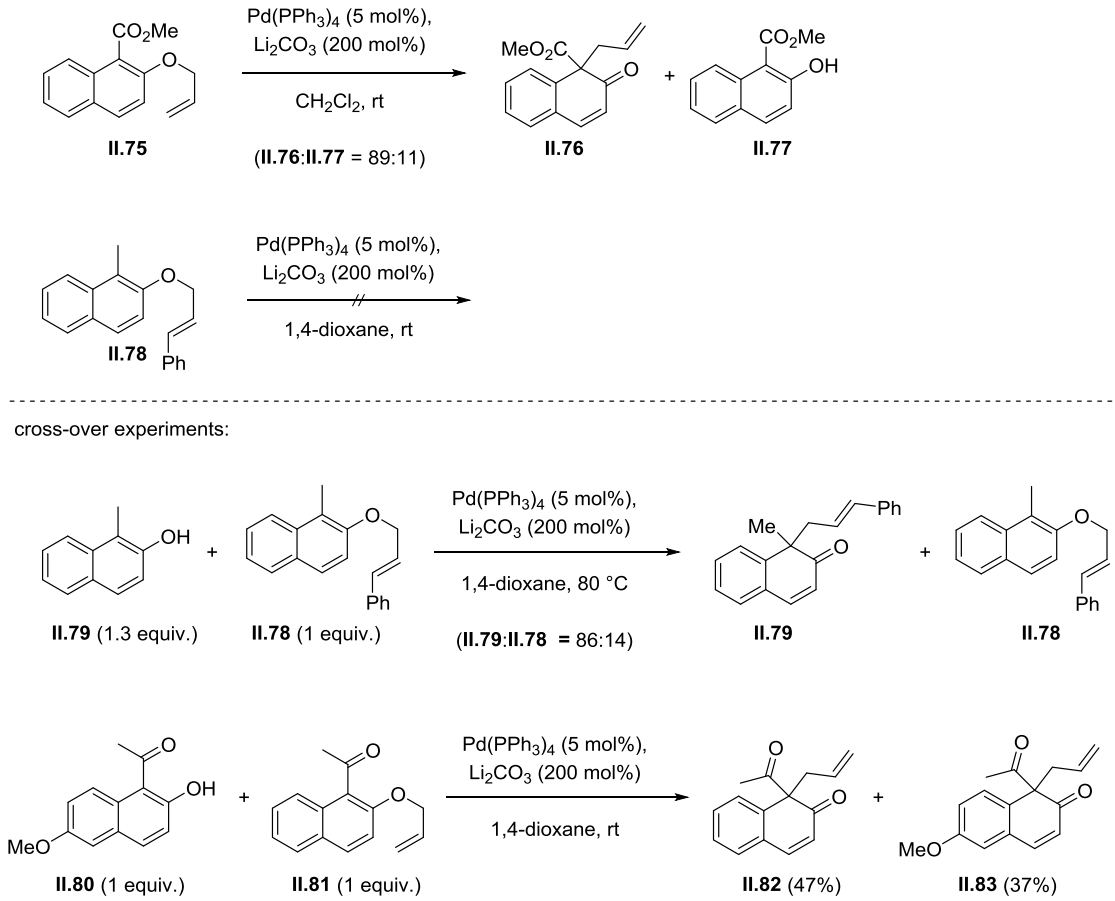
In 2012, Stoltz and co-worker published extensive DFT calculations to get a deeper insight into the mechanism – inner or outer sphere recombination of the enolate and the π-allylpalladium complex – of the asymmetric Tsuji allylation (Scheme 79). They concluded that the inner sphere mechanism explains the observed enantioselectivity better than the outer sphere mechanism. Their calculations indicate the appearance of a 5-coordinate Pd-species **II.70** which undergoes a ligand rearrangement to form intermediate **II.72**. The reductive elimination occurs via an unconventional seven-centered transition state **II.73** in contrast to the standard three-centered carbon-carbon reductive elimination. Although it was not possible to irrevocably determine the enantioselective step, all calculations show that the inner sphere pathway is energetically preferred over the outer sphere one.[170]



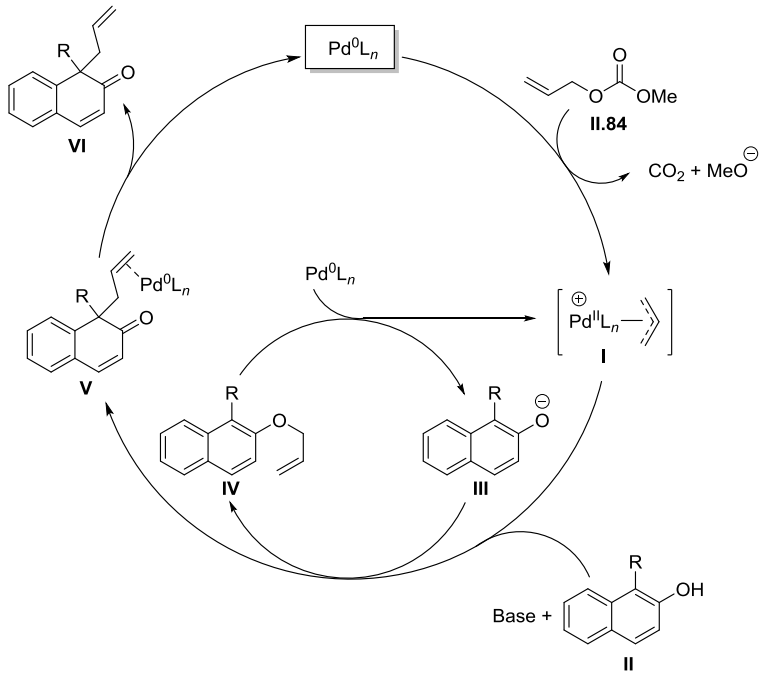
Scheme 79 DFT-calculations for the asymmetric Tsuji-allylation.

You, who published the first Pd-catalyzed intermolecular asymmetric allylic dearomatization[72] performed also mechanistic studies for this reaction (Scheme 80). Treatment of allyl ether **II.75** with $Pd(PPh_3)_4$ afforded the dearomatized product **II.76** and naphthol **II.77** in a ratio of 89 : 11. Test reactions revealed that without Pd-catalyst no reaction was observed. Another test reaction showed that no back reaction from the dearomatized product **II.76** to enol ether **II.75** is possible. NMR studies of the intermolecular dearomatization displayed the *O*-allylated naphthol to be an intermediate of the reaction which fully converts to the product. Interestingly, the *O*-allylated naphthol **II.78** did not react at all with $Pd(PPh_3)_4$. This indicates that the induced effect of the substituent at the C1-position influences the reversible ionization of the allyl ether. However, cross-over experiments with **II.78** and a slight excess of the free naphthol **II.79** afforded the dearomatized product **II.79** as major product. The result of another cross-over experiment proved that the formal rearrangement of the *O*-allylated naphthol is neither an intramolecular nor a contact ion pair process.[164]

Based on the results of these experiments, You proposed a catalytic cycle (Scheme 81). At the beginning, oxidative addition of Pd(0) to allyl carbonate **II.84** generates a π-allylpallydium species. This forms by nucleophilic attack of naphthol **II** either the dearomatized C-alkylated species **V** or the *O*-alkylated species **IV**. The *O*-allyl ether can undergo another oxidative addition with Pd(0) to start the catalytic cycle again.[164]



Scheme 80 Mechanistic studies of the Pd-catalyzed allylic dearomatization.

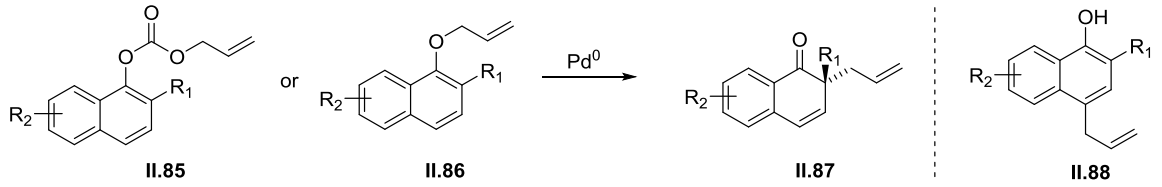


Scheme 81 Proposed catalytic cycle for the decarboxylative allylic dearomatization by You.

5 Results and Discussion*

Although the asymmetric Tsuji allylation and CADA reaction was significantly advanced in the last years, the allylic dearomatization of 2-substituted 1-naphthols by generating an all carbon quaternary center at the C2-position is still unexplored. The most challenging aspect is the accessibility of the *para*-position as the initially dearomatized molecules have the possibility to rearomatize by a formal Cope rearrangement, or the allylation occurs at the *para*-position of the aromatic compound. This would lead to the thermodynamically more stable 2,4-disubstituted 1-naphthols.

We assumed that if the π-allyl Pd-complex is spatially close enough to the naphthoate, the allylation should occur preferentially at the C2-position (Scheme 82). However, the precondition for this is to prohibit the ion diffusion. Very mild reaction conditions and low temperatures would limit subsequent rearrangement and rearomatization. To fulfill these restrictions, the plan of this thesis was to combine the asymmetric allylation methodologies of Trost and Stoltz with the CADA reaction of You and Zhang.



Scheme 82 General idea for the intramolecular dearomatization of 1-naphthols.

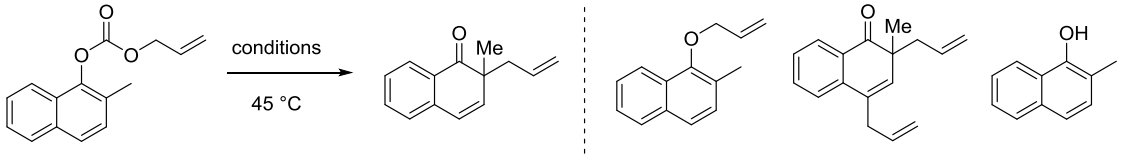
5.1 Screening and Optimization of the Intramolecular CADA Reaction of the Allyl Carbonate of 1-Naphthols

We started the screening with the allyl carbonates of 2-substituted 1-naphthols. Subjecting allyl carbonate **II.89** to $Pd(PPh_3)_4$ in various solvents afforded most of the time the dearomatized product **II.90**, but as an inseparable mixture with the diallylated species **II.92** (Table 22). Naphthol **II.34** was always observed as a side-product. This result indicates on the one hand

* The experiments of chapter II were supported by Bernard (Ruben) Andringa.

that the Cope rearrangement is not suppressed and that on the other hand ion diffusion out of the solvent cages takes place. A second side-product in all reactions was *O*-allylated **II.91**, which is, as before, in accordance to the reaction mechanism proposed by You (Scheme 81). Another interesting fact can be seen by the comparison of entry 3 and 4: surprisingly, the reaction gave better results in non-degassed 1,4-dioxane than in degassed one. However, we have no explanation for this result.

Table 22 Screening of conditions for the racemic dearomatization reaction of allyl carbonate **II.89**.



II.89 **II.90** **II.91** **II.92** **II.34**

entry	catalyst[a]	solvent[b]	result	ratio of **II.90 : II.92**[f]
1	$Pd(PPh_3)_4$	THF	**II.89** + **II.92** (61%)[e]	1 : 0.22
2	$Pd(PPh_3)_4$	*n*-hexane/toluene (1:10)	**II.91**	-
3	$Pd(PPh_3)_4$	1,4-dioxane[c]	**II.89** + **II.92** (37%)[e]	1 : 0.14
4	$Pd(PPh_3)_4$	1,4-dioxane	**II.89** + **II.92** (15%)[e]	1 : 1.1
5	$Pd(PPh_3)_4$	THF[d]	**II.89** + **II.92** (48%)[e]	1 : 0.20
6	$Pd(PPh_3)_4$	CH_2Cl_2	**II.89** + **II.92** (28%)[e]	1 : 1.6
7	$Pd(dba)_2/PPh_3$[g]	THF	-	-

[a] 10 mol% catalyst were used; [b] solvents were degassed via freeze-pump-thaw; 0.05 M; [c] not degassed; [d] 0.02 M solution; [e] isolated as an inseparable mixture; [f] determined by ^{1}H NMR; [g] $Pd(dba)_2$ (5 mol%) and PPh_3 (11 mol%).

To optimize the reaction and thus reduce the amount of side-products, we decided to apply chiral ligands since they are often far more optimized than the racemic ones. The most commonly used chiral ligands are the *P*,*P*-C_2-symmetric-coordinating Trost ligands (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**), (*S*,*S*)-ANDEN-phenyl Trost ligand ((*S*,*S*)-**L3**) and the (*S*,*S*)-DACH-naphthyl Trost ligand ((*S*,*S*)-**L7**), the *P*,*N*-coordinating PHOX ligand (*R*)-*i*-Pr-PHOX ligand ((*R*)-**L5**) (Figure 13) and the *N*,*N*-C_2-symmetric-coordinating Trost ligand (*R*,*R*)-DACH-pyridyl Trost ligand ((*R*,*R*)-**L6**).

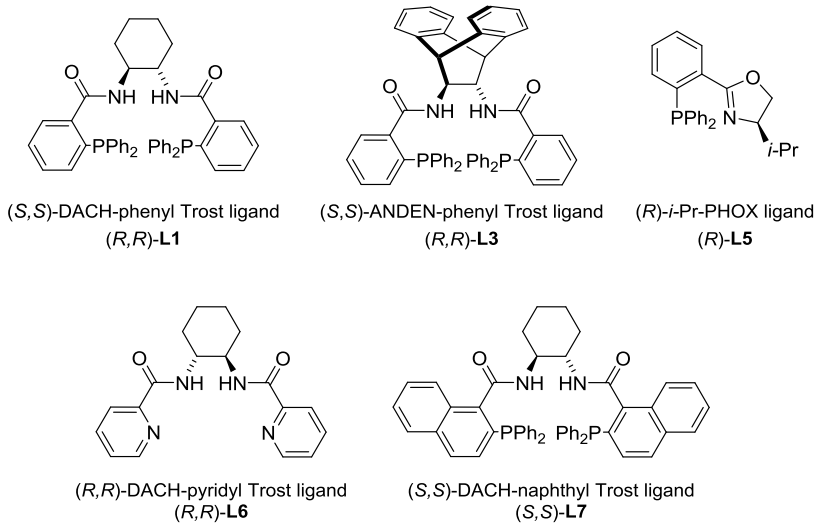
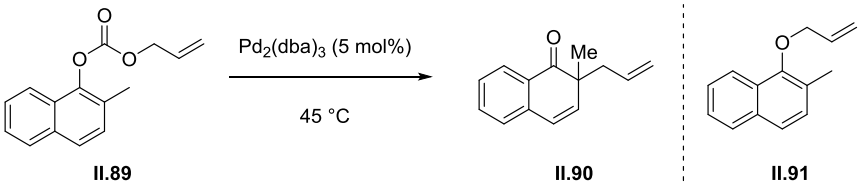


Figure 13 Chiral ligands used for the CADA reaction.

The reactions with (*S*,*S*)-**L3**, (*R*)-**L5** and (*S*,*S*)-**L1** were all screened at 0.083 mmol scale, at a concentration of 0.04 M and at 45 °C (Table 23). The resulting *ee* values of the reactions were determined by chiral HPLC of the isolated clean products. One of the most popular Trost ligands, the (*S*,*S*)-ANDEN-phenyl Trost ligand ((*S*,*S*)-**L3**), resulted only in the formation of allyl ether **II.91** (entries 1–5). Using the (*R*)-*i*-Pr-PHOX ligand afforded the product **II.90** in minor amounts and negligible *ee* (entries 6–10). With the (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**) the yields were still low (entries 11–15) but the obtained *ee* was up to 70% (entry 12). For the two latter ligands, allyl ether **II.91** was always observed as the second product.

Table 23 Ligand screening for the CADA reaction of allyl carbonate **II.89**.



entry	ligand[a]	solvent[b]	result[c]	*ee* [%][d]
1	(*S*,*S*)-**L3**	THF	**II.91**	-
2	(*S*,*S*)-**L3**	toluene	**II.91**	-
3	(*S*,*S*)-**L3**	*n*-hexane/toluene (1:2)	**II.91**	-
4	(*S*,*S*)-**L3**	MTBE	**II.91**	-
5	(*S*,*S*)-**L3**	DME	**II.91**	-

6	(*R*)-**L5**	THF	**II.90** (23%)	6
7	(*R*)-**L5**	toluene	**II.90** (14%)	8
8	(*R*)-**L5**	*n*-hexane/toluene (1:2)	**II.90** (trace)	-
9	(*R*)-**L5**	MTBE	**II.90** (trace)	-
10	(*R*)-**L5**	DME	**II.90** (9%)	-
11	(*S*,*S*)-**L1**	THF	**II.90** (12%)	58
12	(*S*,*S*)-**L1**	toluene	**II.90** (18%)	70
13	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)	**II.90** (31%)	60
14	(*S*,*S*)-**L1**	MTBE	**II.90** (24%)	62
15	(*S*,*S*)-**L1**	DME	**II.90** (trace)	-

[a] 11 mol% ligand were used; [b] solvents were degassed via freeze-pump-thaw; 0.04 M; [c] traces determined by ^{1}H NMR of the crude reaction mixture; [d] determined by chiral HPLC analysis.

Since the (*S*,*S*)-**L1** ligand seemed to be the best, the influence of different concentrations of $Pd_2(dba)_3$ was compared (Table 24). As expected, the best *ee* was obtained with low catalyst loading (entry 1) and the best yield with the higher catalyst loading (entry 2). However, with 100 mol% catalyst, the yield was still just 49% (entry 3). The allyl ether was this time not detected as second main product, but presumably the rearomatized Cope product.

Table 24 Screening of different amounts of catalyst.

II.89 **II.90**

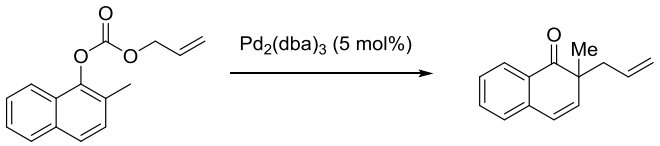
entry	catalyst	ligand	result	*ee*[a]
1	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (11 mol%)	**II.90** (31%)	60%
2	$Pd_2(dba)_3$ (10 mol%)	(*S*,*S*)-**L1** (22 mol%)	**II.90** (55%)	50%
3	$Pd_2(dba)_3$ (100 mol%)	(*S*,*S*)-**L1** (200 mol%)	**II.90** (49%)	32%

[a] determined by chiral HPLC analysis; the solvents were degassed via freeze-pump-thaw; 0.04 M.

In parallel, the influence of the temperature was studied (Table 25). As expected, the yield increased considerably when the reaction was heated to 60 °C and the *ee* decreased from 60% to 44% (entry 1 compared to Table 24, entry 1). An interesting observation was made, when the

solvents for the reaction were used without degassing (entry 2 compared to Table 24, entry 1). Thus, the *ee* decreased only to 52%, but as before, we have no explanation for this result. The reaction was also run at ambient temperature (entry 3), but the product was only isolated in minor amounts albeit in 64% *ee*.

Table 25 Screening the behavior of the CADA reaction at different temperatures.



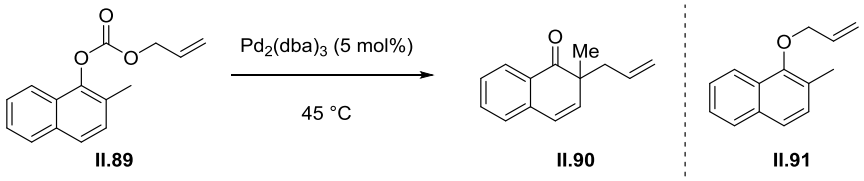
II.89 **II.90**

entry	ligand[a]	solvent[b]	T [°C]	result	*ee* [%][c]
1	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)[d]	60	**II.90** (67%)	44
2	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)	60	**II.90** (67%)	52
3	(*S*,*S*)-**L1**	benzene	23	**II.90** (26%)	64

[a] 11 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] determined by chiral HPLC analysis; [d] solvent was degassed via freeze-pump-thaw.

To improve both the yield and the *ee* of the CADA reaction of allyl carbonate **II.89**, another solvent screening was performed with ligand (*S*,*S*)-**L1**, but this time with the focus on aromatic solvents (Table 26). Benzene as well as chlorobenzene, pyridine, trifluorotoluene and toluene were tested and all of them were used without degassing. The best yield (70%) was obtained with benzene but the *ee* was moderate (entry 1). A far better *ee* (66%) was achieved in toluene, although with poor yield (entry 6). Since benzene gave superior yields, this solvent was used to test the influence of the additives LiCl and DBU on the reaction outcome (entry 7 and 8). The addition of 1 equivalent of LiCl increased the yield from 70% to 83% and left the *ee* unchanged (entry 7). A catalytic amount of DBU increased the *ee* to 68%, but decreased the yield to 28%. Again, **II.91** was a side-product for all reactions.

Table 26 Screening of aromatic solvents and additives.



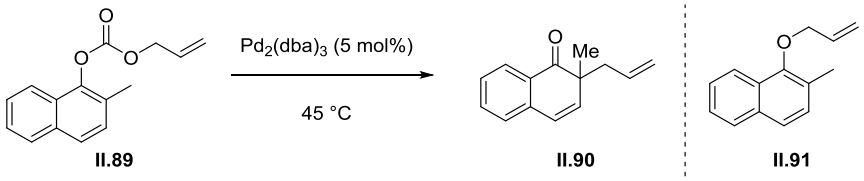
II.89 II.90 II.91

entry	ligand[a]	solvent[b]	additive	result	*ee* [%][c]
1	(*S*,*S*)-**L1**	benzene	-	**II.90** (70%)	42
3	(*S*,*S*)-**L1**	chlorobenzene	-	**II.90** (60%)	42
4	(*S*,*S*)-**L1**	pyridine	-	**II.90** (24%)	46
5	(*S*,*S*)-**L1**	trifluorotoluene	-	**II.90** (15%)	46
6	(*S*,*S*)-**L1**	toluene	-	**II.90** (18%)	66
7	(*S*,*S*)-**L1**	benzene	LiCl (1 equiv)	**II.90** (83%)	44
8	(*S*,*S*)-**L1**	benzene	DBU (0.1 equiv)	**II.90** (28%)	68

[a] 11 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] determined by chiral HPLC analysis; [d] solvent was degassed via freeze-pump-thaw.

Since all the results with ligand (*S*,*S*)-**L1** gave either good yields or *ee* but not both at the same time the two remaining DACH ligands (*R*,*R*)-**L6** and (*S*,*S*)-**L7** were screened for the CADA reaction of **II.89** (Table 27). Unfortunately (*R*,*R*)-**L6** did not even fully decarboxylate allyl carbonate **II.89** (entries 1–3). In contrast to this, the naphthyl ligand (*S*,*S*)-**L7** afforded in all the screened solvents the product **II.90** with *ee* values of around 70%; however, the received yields were low (entries 4–7).

Table 27 Screening of further ligands for the CADA reaction of allyl carbonate **II.89**.



II.89 II.90 II.91

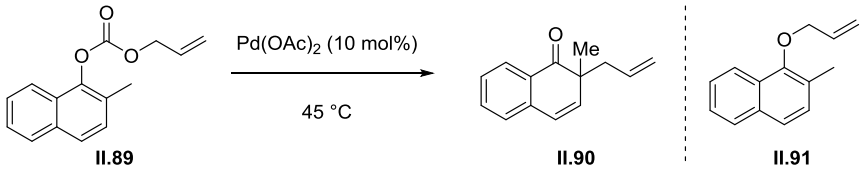
entry	ligand[a]	solvent[b]	result	*ee* [%][c]
1	(*R*,*R*)-**L6**	benzene	**II.89, II.91** (trace)[d]	-
2	(*R*,*R*)-**L6**	toluene	**II.89, II.91** (trace)[d]	-
3	(*R*,*R*)-**L6**	THF	**II.89, II.91** (trace)[d]	-
4	(*S*,*S*)-**L7**	benzene	**II.90** (12%)	70

5	(*S*,*S*)-**L7**	toluene	**II.90** (6%)	71
6	(*S*,*S*)-**L7**	chlorobenzene	**II.90** (24%)	70
7	(*S*,*S*)-**L7**	*n*-hexane/toluene (1:2)	**II.90** (18%)	69

[a] 11 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] determined by chiral HPLC analysis; [d] determined by crude ^{1}H NMR.

Furthermore, we faced problems with the reproducibility of these reactions. Sometimes the active catalyst degraded too fast, distinguishable by the formation of a suspension from the previous clear solution. Thus, we also investigated the use of the Pd(II)-source $Pd(OAc)_2$ instead of $Pd_2(dba)_3$. Various solvents were again screened, but the determined yields were all low to mediocre and the main product was always the *O*-allylated naphthol **II.91** (Table 28). Sometimes, allyl carbonate **II.89** did not even fully decarboxylate (entries 9 and 10). As before, reactions with degassed solvents (entries 1 and 13) showed lower yields when compared to the corresponding non-degassed solvents (entries 2 and 12). However, the poor reproducibility did not improve when $Pd(OAc)_2$ was used.

Table 28 Screening of solvents with $Pd(OAc)_2$ as catalyst.



1	ligand[a]	solvent[b]	result[c]
1	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)[d]	**II.90** (8%) + **II.91** (40%)
2	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)	**II.90** (11%) + **II.91** (46%)
3	(*S*,*S*)-**L1**	benzene	**II.90** (11%) + **II.91** (51%)
4	(*S*,*S*)-**L1**	chlorobenzene	**II.90** (12%) + **II.91** (71%)
5	(*S*,*S*)-**L1**	toluene	**II.90** (17%) + **II.91** (83%)
6	(*S*,*S*)-**L1**	1,4-dioxane	**II.90** (21%) + **II.91** (57%)
7	(*S*,*S*)-**L1**	1,2-dichloroethane	**II.90** (9%) + **II.91** (72%)
8	(*S*,*S*)-**L1**	trifluorotoluene	**II.90** (6%) + **II.91** (62%)
9	(*S*,*S*)-**L1**	CPME[d]	**II.90** (2%) + **II.91** (6%) + **II.89** (69%)
10	(*S*,*S*)-**L1**	DME[d]	**II.90** (15%) + **II.91** (67%) + **II.89** (6%)
11	(*S*,*S*)-**L1**	CH_3CN[d]	**II.90** (8%) + **II.91** (70%)
12	(*S*,*S*)-**L1**	CH_2Cl_2	**II.90** (41%) + **II.91** (47%)
13	(*S*,*S*)-**L1**	CH_2Cl_2[d]	**II.90** (20%) + **II.91** (62%)

[a] 10 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] yield was determined by ^{1}H NMR ($CDCl_3$, 400 or 600 MHz, dimethyl sulfone-d_6 as internal standard); [d] solvents were degassed via freeze-pump-thaw.

In each of the screenings, *O*-allylated naphthol **II.91** was observed as the side or even main product. Therefore, we started to think about the reaction mechanism and at which point the dearomatized product **II.90** and ether **II.91** were formed. Were they both formed at the same time or was **II.91** formed first and then rearranged to **II.90**? How fast is the decarboxylation of the carbonate? To clarify those questions, a ^{1}H NMR experiment was performed (Figure 14). The reaction was set up as usual, but after addition of the starting material **II.89** to the catalyst solution, aliquots were taken out of the reaction mixture after 1, 2, 5, 20 and 40 min and after 1.5 and 4.5 h. The samples were filtered through a short plug of silica gel, washed with diethyl ether and concentrated. Remarkably, **II.89** decarboxylated in less than one minute and only ether **II.91** and very small amounts of product **II.90** are visible. The following samples show increased signals for **II.90** until 20 min and then the relative intensities of **II.90** to **II.91** do not change any more. This led to the conclusion that the decarboxylation is in fact extremely fast and **II.91** is most likely formed first by *O*-alkylation. The second step is then the formation of the product, presumably via a palladium catalyzed Claisen rearrangement. However, there is no explanation why the reaction stopped after a certain time and no further conversion of **II.91** to **II.90** took place.

Based on these observations and results in combination with the catalytic cycles of Stoltz and You we tried to come up with a catalytic cycle for the intramolecular CADA reaction of 1-naphthol derivatives. Our proposed mechanism is depicted in Scheme 83 and illustrates numerous pathways toward the dearomatized product **II.90**. The first step is the oxidative addition of Pd(0) to allyl carbonate **II.89** to form the Pd(II)-π-allyl complex **I**. This complex can undergo a cross-over to separate the ion-pair. Both complexes **I** and **II** can decarboxylate and generate **III** and **IV** respectively, which can be transferred into each other by another cross-over. For the final yield of the reaction it might not be important which decarboxylation pathway is the actual one, yet it might influence the *ee*. The *O*-Pd(II)-π-allyl complex **IV** can either undergo reductive elimination to *O*-allylated naphthol **II.91**, which was detected in almost every reaction and can be converted to **IV** again by oxidative addition of Pd(0). Or complex **IV** can undergo a different reductive elimination to form the dearomatized product **II.90** and simultaneously regenerate the Pd(0)-species. Additionally, ion pair **III** could generate the product by an S_N2' attack of the naphtholate at the Pd(II)-π-allyl complex.

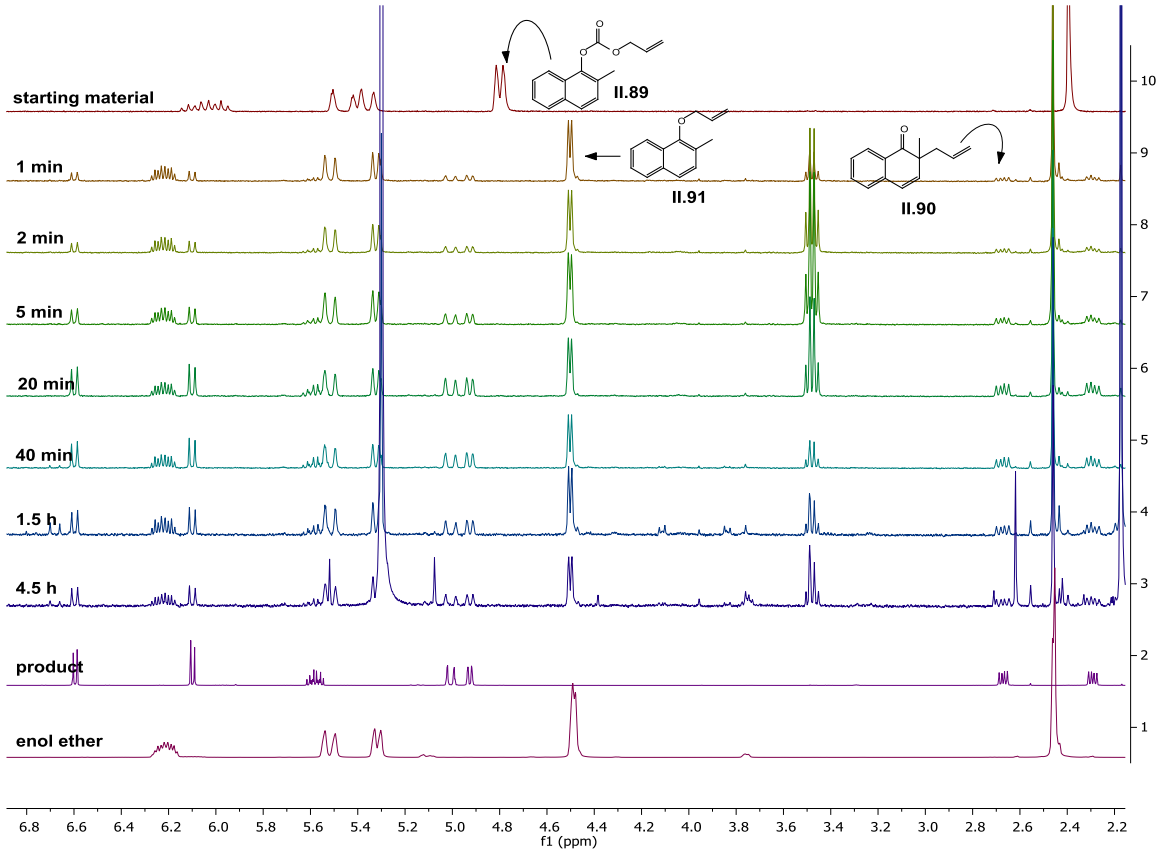
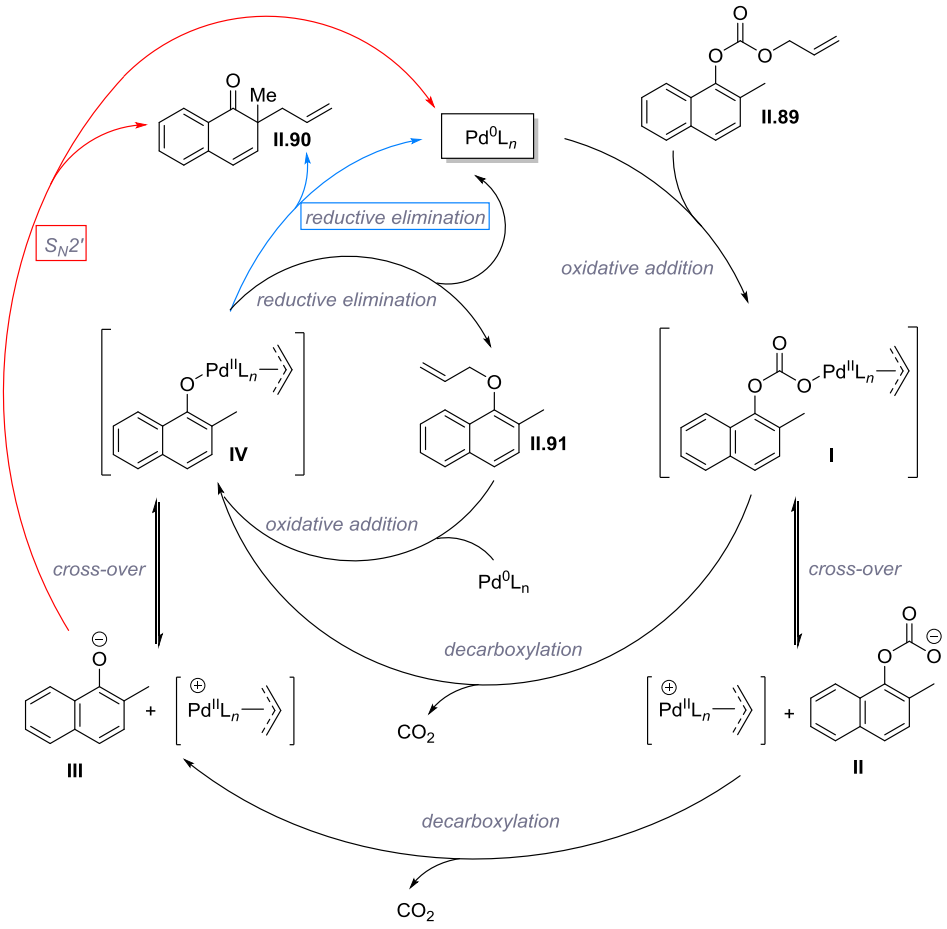


Figure 14 ^{1}H NMR experiment ($CDCl_3$, 400 MHz); reaction conditions: $Pd_2(dba)_3$ (5 mol%), (*S*,*S*)-DACH-phenyl Trost ligand (11 mol%), LiCl (1 equiv), benzene (non-degassed), 45 °C.

Evidence that at least one of the two possible cross-overs take place in the racemic allylic dearomatization with $Pd(PPh_3)_4$ is the observation of the diallylated side-product **II.92** together with the completely de-allylated naphthol **II.34**. Since the second allylation seems to be suppressed when using the chiral ligands, the ion-diffusion might be inhibited by them. To gain further insights into the mechanism, substituted and/or deuterated allyl carbonates and naphthols would have to be synthesized and subjected to various conditions to see if scrambling takes place and if an inner- or outer-sphere mechanism is more likely.



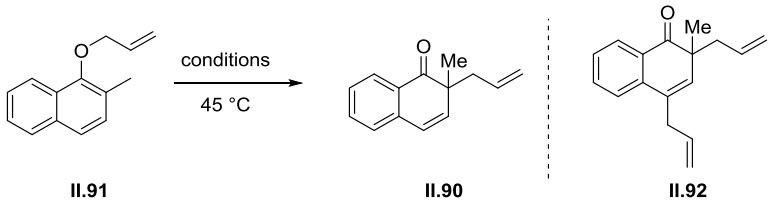
Scheme 83 Proposed mechanism for the intramolecular CADA reaction of allyl carbonate **II.89**.

5.2 Screening and Optimization of the Intramolecular CADA Reaction of Allyl Naphthol Ethers

As a result of the screenings and the NMR experiment we decided to simplify our reaction system in such a way that the allyl ether **II.91** was used directly instead of the allyl carbonate **II.89**. Thus, the decarboxylation step would be omitted and the mechanism simplified.

The screening of the best conditions for the dearomatization of the allyl naphthol started in the same way as with the allyl carbonate. First of all, the racemic dearomatization with $Pd(PPh_3)_4$ was tested with various solvents (Table 29). Overall, the yields were slightly better than with the carbonate, but still an inseparable mixture of **II.90** and **II.92** was isolated. Again, the comparison of degassed and non-degassed dioxane (entries 2 and 3) showed a better result for the non-degassed solvent.

Table 29 Screening of conditions for the racemic dearomatization reaction of allyl ether **II.91**.



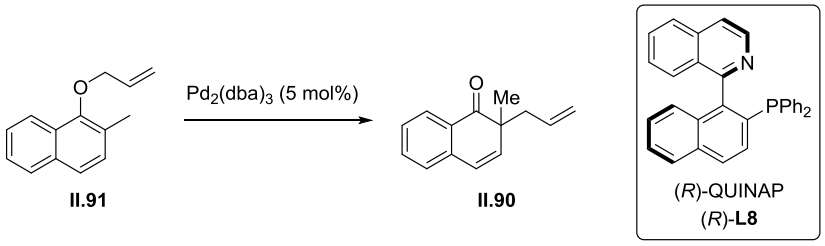
II.91 **II.90** **II.92**

entry	catalyst[a]	solvent[b]	result	ratio of II.90 : II.92[f]
1	$Pd(PPh_3)_4$	*n*-hexane/toluene (1:10)	**II.91**	-
2	$Pd(PPh_3)_4$	1,4-dioxane[c]	**II.90** + **II.92** (45%)[e]	1 : 0.24
3	$Pd(PPh_3)_4$	1,4-dioxane	**II.90** + **II.92** (38%)[e]	1 : 0.50
4	$Pd(PPh_3)_4$	THF[d]	**II.90** + **II.92** (47%)[e]	1 : 0.27
5	$Pd(PPh_3)_4$	CH_2Cl_2	**II.90** + **II.92** (34%)[e]	1 : 0.92
6	$Pd(dba)_2$, PPh_3[g]	THF	-	-

[a] 10 mol% catalyst were used; [b] solvents were degassed via freeze-pump-thaw; 0.04 M; [c] not degassed; [d] 0.02 M solution; [e] isolated as an inseparable mixture; [f] determined by ^{1}H NMR spectroscopy; [g] $Pd(dba)_2$ (5 mol%) and PPh_3 (11 mol%).

We then changed to chiral ligands and began with the (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**) (Table 30). The *ee* of all reactions turned out to be independent of the reaction conditions and was always around 60% (entries 1–4). The best isolated yield was observed for entry 1 with 84%. With the (*S*,*S*)-ANDEN-phenyl Trost ligand ((*S*,*S*)-**L3**) no conversion could be detected (entries 5 and 6). The (*S*,*S*)-DACH-naphthyl Trost ligand ((*S*,*S*)-**L7**) afforded the highest *ee* with 78% but the yields were low (entries 7–10). Additionally to the well-established ligands, the (*R*)-QUINAP ligand (*R*)-**L8** was tested, yet with no success (entry 11). The yield was only 19% and no *ee* at all was detected. All these results are in accordance with the previous ones of the allyl carbonate **II.89**: (*S*,*S*)-**L1** provides good yields, (*S*,*S*)-**L7** good *ee*'s and (*S*,*S*)-**L3** is not able to undergo an oxidative addition to the allyl ether. However, a still ongoing challenge is the combination of a good yield and *ee* in one experiment.

Table 30 Screening of conditions for the CADA reaction of allyl naphthol **II.91**.

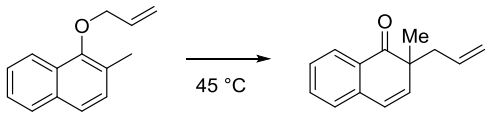


entry	ligand[a]	solvent[b]	T [°C]	result [%][c]	*ee* [%][d]
1	(*S*,*S*)-**L1**	benzene	45	**II.90**: 88 (84)	59
2	(*S*,*S*)-**L1**	benzene[e]	45	**II.90**: 84 (76)	-
3	(*S*,*S*)-**L1**	benzene	35	**II.90**: 69 (68)	60
4	(*S*,*S*)-**L1**	benzene	23	**II.90**: 62 (57)	62
5	(*S*,*S*)-**L3**	benzene	45	**II.91**	-
6	(*S*,*S*)-**L3**	1,4-dioxane	45	**II.91**	-
7	(*S*,*S*)-**L7**	benzene	45	**II.90**: 17 (16)	78
8	(*S*,*S*)-**L7**	benzene[e]	45	**II.90**: 18	-
9	(*S*,*S*)-**L7**	1,4-dioxane	45	**II.90**: 25 (24)	73
10	(*S*,*S*)-**L7**	1,4-dioxane[e]	45	**II.90**: 18	-
11	(*R*)-**L8**[f]	THF[e]	45	**II.90**: (19)	0

[a] 11 mol% ligand was used; [b] solvents were not degassed; 0.05 M; [c] yield was determined by ^{1}H NMR ($CDCl_3$, 400 or 600 MHz, dimethyl sulfone-d_6 as internal standard); yield in parentheses refer to isolated yield; [d] determined by chiral HPLC analysis of the isolated product; [e] solvents were degassed via freeze-pump-thaw; [f] 12.5 mol% ligand were used.

Thus, we tried to optimize the ratio of the catalyst to the ligand (Table 31). The best result was obtained with 4 mol% catalyst and 8.8 mol% ligand (entry 5), however, the yield was similar to the conditions, which were used before and the *ee* was even lower. Therefore, the screening did not lead to optimization of the reaction.

Table 31 Screening for different catalyst to ligand ratios.



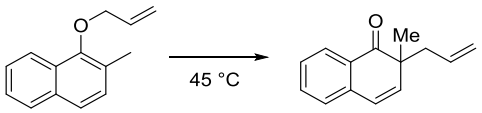
II.91 **II.90**

entry	catalyst	ligand	solvent[a]	result [%][b]	*ee* [%][c]
1	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (10 mol%)	benzene[d]	**II.90**: 72 (76)	53
2	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (9 mol%)	benzene[d]	**II.90**: traces	-
3	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (9 mol%)	benzene	**II.90**: 36 (33)	60
4	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (8 mol%)	benzene[d]	**II.91**	-
5	$Pd_2(dba)_3$ (4 mol%)	(*S*,*S*)-**L1** (8.8 mol%)	benzene	**II.90**: 85 (87)	49
6	$Pd_2(dba)_3$ (3 mol%)	(*S*,*S*)-**L1** (6.6 mol%)	benzene[d]	**II.90**: 76	-
7	$Pd_2(dba)_3$ (3 mol%)	(*S*,*S*)-**L1** (6.6 mol%)	benzene	**II.90**: 66 (56)	61

[a] solvents were not degassed; 0.05 M; [b] yield was determined by ^{1}H NMR ($CDCl_3$, 400 or 600 MHz, dimethyl sulfone-d_6 as internal standard); yields in parentheses refer to isolated yields; [c] determined by chiral HPLC analysis of the isolated product; [d] solvents were degassed via freeze-pump-thaw.

In addition to this experiment and due to the fact that reproducibility was still a problem, we also investigated other Pd-catalysts such as $Pd(OAc)_2$, $Pd(t\text{-}Bu_3P)_2$, $Pd(dppe)_2$ and $Pd(dmdba)_2$ (Table 32). The first three catalysts, $Pd(OAc)_2$, $Pd(t\text{-}Bu_3P)_2$ and $Pd(dppe)_2$, did not show any reactivity and no conversion of the starting material was observed (entries 1–6). $Pd(dmdba)_2$ in contrast provided the product in up to 68% yield (entry 9) and 48–60% *ee*. Changing the ligand from (*S*,*S*)-**L1** to (*S*,*S*)-**L7** was unsuccessful and no conversion of **II.91** took place (entries 14–16). However, all four catalysts were not able to compete with $Pd_2(dba)_3$.

Table 32 Screening of different catalysts and solvents.



II.91 **II.90**

entry	catalyst[a]	ligand[b]	solvent[c]	result[d]	*ee* [%][d]
1	$Pd(OAc)_2$	(*S*,*S*)-**L1**	benzene	**II.91**	-
2	$Pd(OAc)_2$	(*S*,*S*)-**L1**	benzene/CH_2Cl_2	**II.91**	-
3	$Pd(OAc)_2$	(*S*,*S*)-**L1**	CH_2Cl_2	**II.91**	-

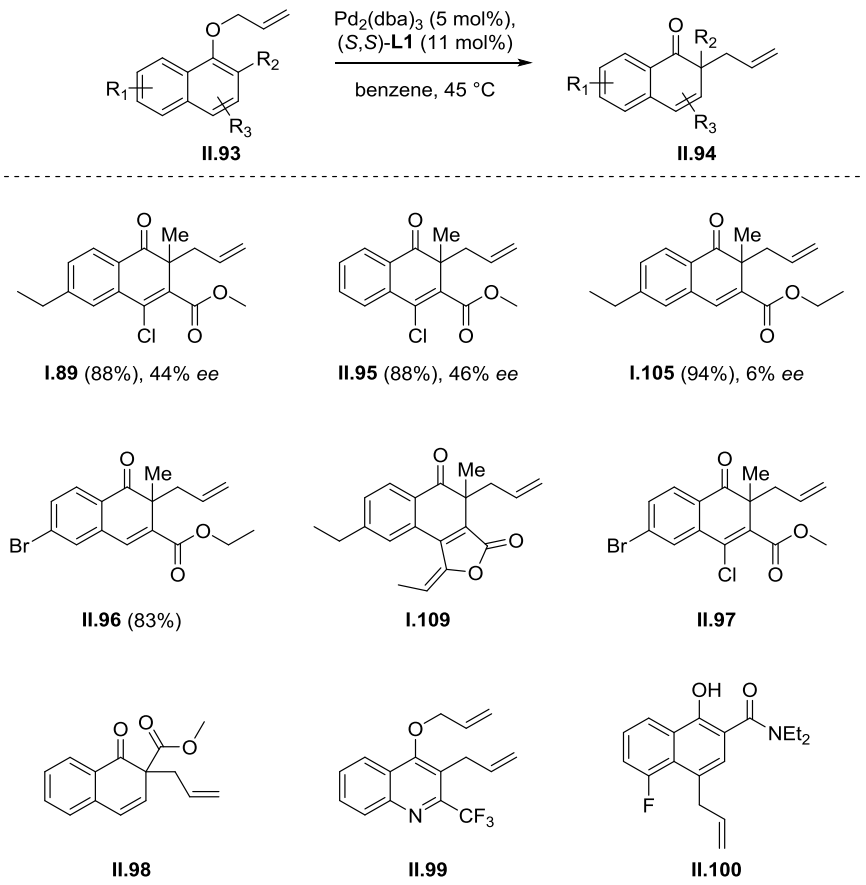
4	$Pd(OAc)_2$	(*S*,*S*)-**L1**	THF	**II.91**	-
5	$Pd(t\text{-}Bu_3P)_2$	(*S*,*S*)-**L1**	benzene	**II.91**	-
6	$Pd(dppe)_2$	(*S*,*S*)-**L1**	benzene	**II.91**	-
7	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	benzene	**II.90** (41%)	60
8	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	benzene[e]	**II.90** (63%)	60
9	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	toluene	**II.90** (68%)	57
10	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	toluene[e]	**II.90** (47%)	55
11	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	1,4-dioxane	**II.90** (55%)	55
12	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	THF	**II.90** (traces)	-
13	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	1,2-dichlorobenzene	**II.90** (60%)	48
14	$Pd(dmdba)_2$	(*S*,*S*)-**L7**	benzene	**II.91**	-
15	$Pd(dmdba)_2$	(*S*,*S*)-**L7**	toluene	**II.91**	-
16	$Pd(dmdba)_2$	(*S*,*S*)-**L7**	1,4-dioxane	**II.91**	-

[a] 10 mol% catalyst were used; [b] 11 mol% ligand was used; [c] solvents were not degassed; 0.05 M; [d] determined by chiral HPLC analysis of the isolated product; [e] solvents were degassed via freeze-pump-thaw. dmdba = 3,5,3',5'-dimethoxydibenzylideneacetone.

5.3 Substrate Scope of the Intramolecular CADA Reaction of 1-Naphthols

Although the screenings did not afford optimal conditions for the intramolecular CADA reaction of C2-substituted 1-naphthols, a few substrates with different substitution patterns were synthesized. The adopted conditions are depicted in Scheme 84. All reactions were carried out at 0.1 mmol scale and as a 0.05 M solution in benzene. The three products **I.89**, **II.95** and **I.105** could be isolated in very good yields, yet only in very low to moderate *ee*. For the brominated substrate **II.96**, which was obtained in 83% yield, the *ee* could not be determined due to insufficient separation by HPLC. The crude ^{1}H NMR of tricyclic lactone **I.109** showed full conversion toward the product, but unfortunately the dba ligand turned out to be co-polar with the product **I.109** and thus purification and determination of the *ee* was impossible. A similar problem appeared for **II.97** and **II.98**. The crude ^{1}H NMR showed conversion toward the products, albeit imperfect, but the dearomatized products and the corresponding starting materials appeared to be co-polar. A heterocyclic substrate was tested as well, but the quinoline derivative **II.99** did not undergo any reaction at all. Last but not least a fluorinated amide was subjected to the CADA conditions, but instead of the dearomatized product, the Cope

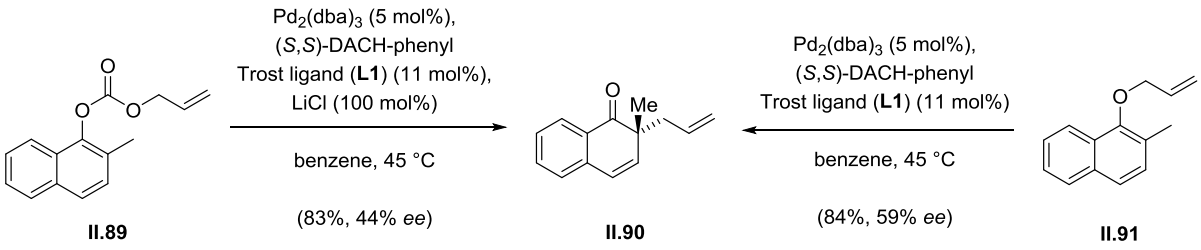
rearrangement product **II.100** was observed. Unfortunately, it could not be isolated, since it was co-polar with the dba.



Scheme 84 Substrate scope of the CADA reaction of 1-naphthols.

6 Conclusion and Outlook

In summary, the development of a Pd-catalyzed allylic dearomatization of 2-methyl-1-naphthols has been investigated in this thesis. We were able to overcome the challenge of rearomatization via subsequent Cope rearrangement by utilizing mild and neutral conditions. Diallylation caused by ion diffusion was obviated by the use of more elaborate chiral ligands. Initial screenings with allyl carbonate **II.89** gave yields up to 83% (Scheme 85), and the reaction was also analyzed by NMR spectroscopy. These studies revealed that the decarboxylation reaction occurred rapidly and resulted in the in the formation of the *O*-allylated naphthyl ether, which was then converted to the product. Based on this and previous results, a mechanism was proposed for the intramolecular CADA reaction of 1-naphthols.



Scheme 85 Intramolecular CADA reaction of 1-naphthols.

The second part of the screenings was performed with allyl naphthyl ether **II.91** which afforded overall slightly higher yields and *ee* values as compared to the carbonate. However, the observed *ee* values were still moderate. The best *ee* values (up to 78%) were in general obtained with the (*S*,*S*)-DACH-naphthyl Trost ligand ((*S*,*S*)-**L7**), yet with poor yields. This proved to be an ongoing problem throughout the screenings. We therefore primarily focused on the optimization of the yield of the allylation. The best conditions were tested with a few substrates, and dearomatized products were obtained in yields of 83–94%. The only drawback was the difficult product isolation due to similar polarities of starting material and ligand of the used precatalyst.

Future efforts would involve screenings with (*S*,*S*)-DACH-naphthyl Trost ligand ((*S*,*S*)-**L7**) in combination with more additives ((chiral) Lewis acids, salts, bases, etc.) to enhance the *ee* and yields. It would also be interesting and helpful to gain deeper insight into the mechanism of the

dearomatization reaction. Thus, labeling and cross-over experiments, similar to the ones of Trost and Stoltz (see introduction), would be useful. To perform all those experiments in a reproducible form, it would be necessary to conduct the experiments in a glove box.

CHAPTER III

CLAISEN REARRANGEMENT OF ALLYL CHLOROVINYL ETHERS

7 Introduction†

Within the family of commercially available trihaloethene derivatives, 1,1,2-trichloroethene (**III.20**, TCE, b.p. 87 °C) is by far the most commonly used reagent. Dr. E. Fischer (not Hermann Emil Fischer) achieved the first synthesis of **III.20** in 1864 by reductive dehalogenation of hexachloroethane with hydrogen.[171] Since then, TCE (**III.20**) has gained major importance in various industrial applications.[172] The ease of preparation of large quantities of this non-flammable, volatile organic compound led to a staggering global consumption of 428.6×10^3 t in 2011. Of this, 84% of the total production volume in the USA were used as an intermediate for manufacturing the refrigerant 1,1,1,2-tetrafluoroethane (HFC-134a) and 15% as a solvent for metal degreasing.[172,173] TCE (**III.20**) is classified as human carcinogen, and its toxicity has been investigated and discussed in detail.[173,174] Amongst other factors, the toxicity associated with **III.20** has led to continuously decreasing production rates in the industry.[172,175]

Since the preparation of **III.20** has been extensively studied over the years, only a selection of approaches will be provided. There are several feedstock chemicals that can be used to synthesize TCE (**III.20**). One such feedstock is acetylene, which is converted to **III.20** via a chlorination-dehydrochlorination pathway.[172] A different approach is the oxychlorination of ethene to afford **III.20**. In this reaction, the chlorine source is hydrogen chloride, which is oxidized according to the Deacon process.[172,176,177] Tetrachloroethene can also be converted into TCE (**III.20**) via hydrogenolysis with transition metal catalysts.[178]

Trihaloethenes in general are versatile C_2-building blocks that can be simply modified via addition, elimination and transition metal-catalyzed reactions (Figure 15).

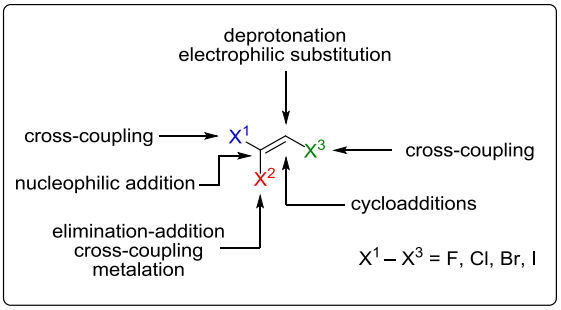
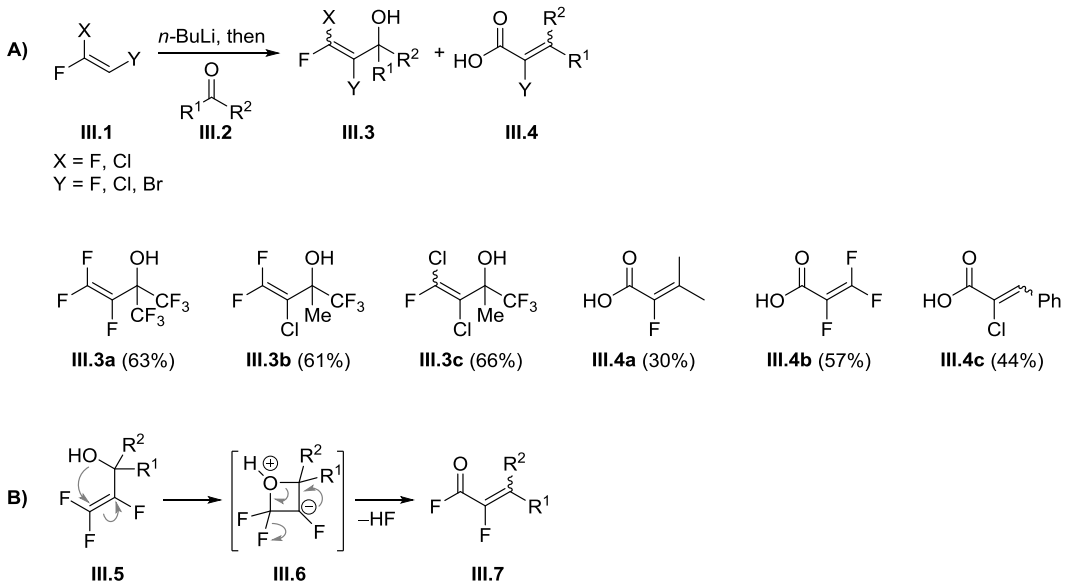


Figure 15 Overview over the reactivity of trihaloethenes.

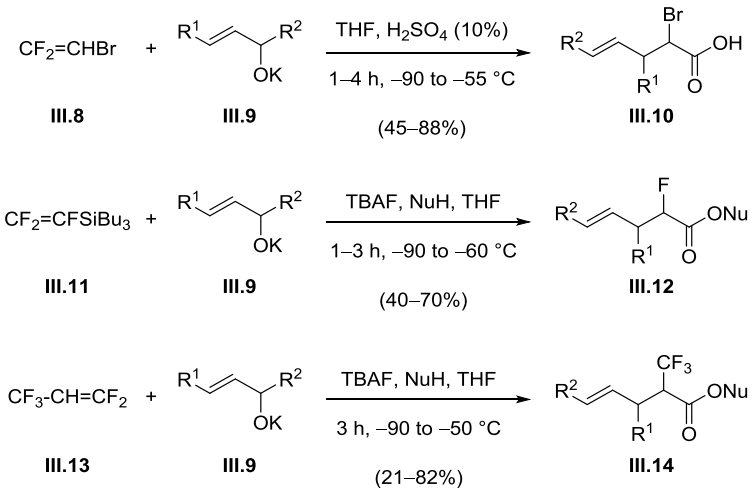
† The introduction of chapter III has been adapted from the review *"Trihaloethenes as Versatile Building Blocks for Organic Synthesis"* - A. S. Grossmann, T. Magauer*, *Org. Biomol. Chem.* **2016**, *14*, 5377–5389.

An example for an addition reaction was published by Tarrant et al. They prepared fluorine-containing vinyllithium reagents using **III.1**. Treatment with a variety of carbonyl compounds **III.2** afforded the corresponding 1,2-addition products **III.3** and **III.4** (Scheme 86).[179]



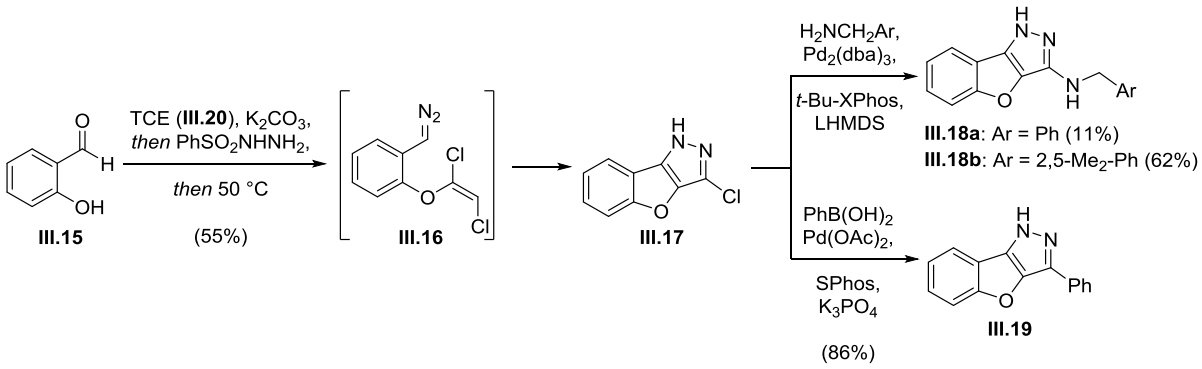
Scheme 86 a) 1,2-Addition of trihalovinyllithium reagents to carbonyl compounds **III.2**. b) Reaction mechanism for the 1,3-rearrangement of **III.5**.

The group of Tellier has published fundamental work on Claisen rearrangements of halogenated vinyl ether for the synthesis of halogenated acids and esters such as **III.10**, **III.12** and **III.14** (Scheme 87).[180,181,182] The requisite halogenated enol ethers are formed by an addition-elmination reaction of allylic alkoxides **III.9** and halogenated ethylene derivatives **III.8**, **III.11** and **III.13**. Following this strategy, they were able to introduce bromine, fluorine and trifluoromethyl groups at the α-position of an acid or ester.



Scheme 87 Claisen rearrangements of allyl halovinyl ethers.

Mani and Sales discovered an intramolecular 1,3-dipolar cycloaddition one-pot protocol for the concise synthesis of benzofuropyrazoles (Scheme 88).[183] Starting from salicylaldehyde (**III.15**), the corresponding dichlorovinyl ether was generated and treated with benzenesulfonyl hydrazide to form the corresponding hydrazine. Raising the temperature to 50 °C afforded aryldiazomethane **III.16**, which spontaneously cyclized to form chloropyrazole **III.17** in 55% overall yield. The product could be further functionalized by Buchwald–Hartwig or Suzuki–Miyaura cross-coupling reactions.

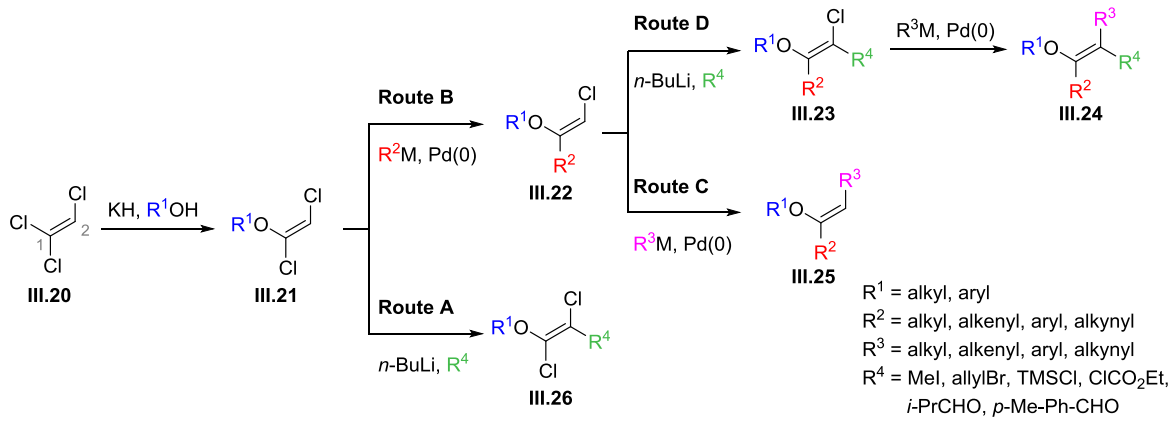


Scheme 88 A one-pot protocol for the synthesis of benzofuropyrazoles.

Since the reactivities of the three C-Cl bonds of TCE (**III.20**) differ significantly from each other, it can be used as versatile reagent for cross-coupling reactions. Hultin exploited the unique reactivity of **III.20** which enabled the preparation of highly substituted ethene derivatives in a controlled fashion (Scheme 89).[184] In each case, the first step involves formation of a (*E*)-1,2-dichlorovinyl ether **III.21** by an elimination-addition reaction. As depicted in route A, deprotonation of the C(2)-H group in **III.21** followed by subsequent addition of an electrophile allows the preparation of substituted 1,2-dichlorovinyl ether **III.26**. In route B, the C(1)-Cl group of **III.21** is able to participate in cross-coupling reactions just as the C(2)-Cl group in the ensuing step (route C). The trisubstituted alkene **III.25** can be obtained via route C. Route D starts from **III.22** as well, but the following step involves the deprotonation of C(2)-H and replacement with an electrophile. A further cross-coupling reaction of the C(2)-Cl group of **III.23** then gives rise to the tetrasubstituted alkene **III.24**.

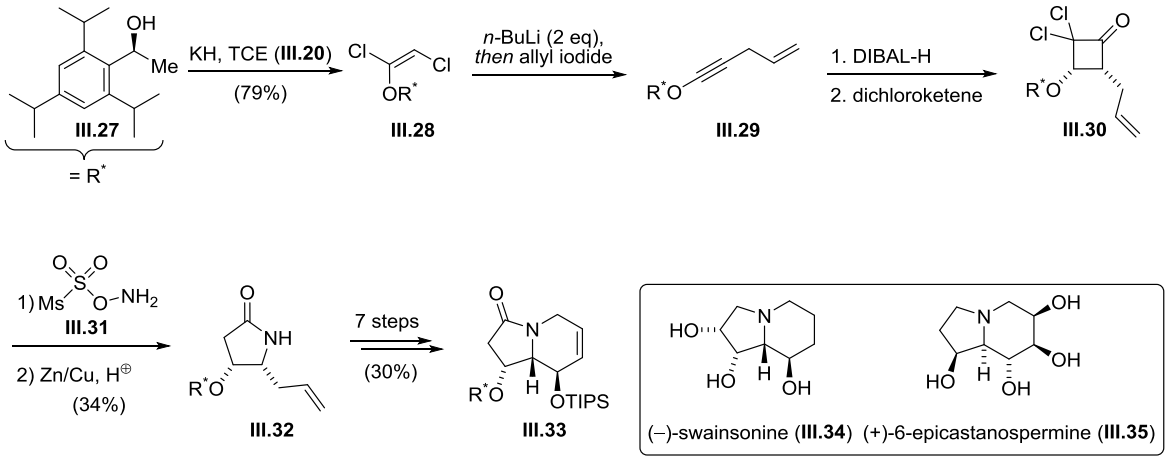
However, there are limitations to the reaction pathways depicted in route A and C. While Suzuki–Miyaura cross coupling reactions at the C(1)-Cl group of product **III.26** (route A) were not stereoselective, Sonogashira cross-couplings proved to be unsuccessful at all. In route C,

deprotonation of the C(2)-H group of **III.25** was problematic and generation of a tetrasubstituted alkene was not possible via this route.[184]



Scheme 89 Reaction sequences for the functionalization of **III.20**.

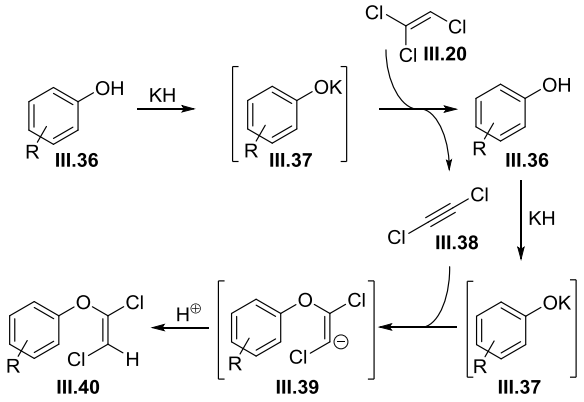
The unique reactivity of the trihaloethenes was also used in the total synthesis of natural products. One example is Poisson's total syntheses of (–)-swainsonine (**III.34**) and (+)-6-epicastanospermine (**III.35**), which started with the preparation of the chiral 1,2-dichloroenol ether **III.28** (Scheme 90).[185] Treatment of **III.28** with two equivalents of *n*-butyllithium gave rise to the corresponding acetylide, which was treated with allyl iodide to afford the ynol ether **III.29**. After selective reduction of the alkine moiety to the *Z*-double bond using DIBAL-H, a [2+2] cycloaddition with *in situ* generated dichloroketene took place, yielding cyclobutanone **III.30**. Tamura's reagent (**III.31**) was then used for the Beckmann ring expansion to yield a dichlorolactam, which was dechlorinated with zinc-copper couple in acidic medium. The so formed pyrrolidinone **III.32** was converted to the indolizidinone **III.33** in seven further steps. (–)-Swainsonine (**III.34**) and (+)-6-epicastanospermine (**III.35**) were prepared in eight and four steps, respectively, from this common indolizidinone precursor.



Scheme 90 Synthesis of an intermediate for the synthesis of (–)-swainsonine (**III.34**) and (+)-6-epicastanospermine (**III.35**).

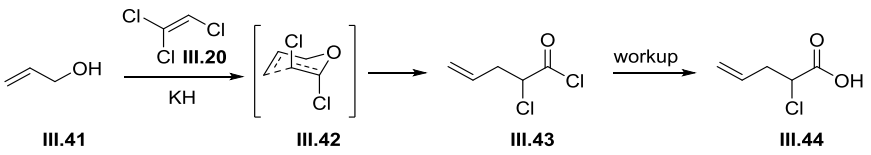
8 Results and Discussion

Prior to this Ph.D. thesis, the synthesis of 2-chloropent-4-enoic acid (**III.44**) from allyl alcohol (**III.41**) and TCE (**III.20**) was already investigated in our group. The envisaged product could be obtained by utilizing a part of a methodology published by Greene in 1987, who reported the synthesis of acetylenic ethers from simple alcohols and TCE (**III.20**).[186] Mechanistically, the reaction commenced with the formation of a 1,2-dichlorovinyl ether, via an elimination-addition sequence. Such transformations, also referred to as condensation[187] or substitution[188,189] reactions, occur readily with TCE (**III.20**). Seminal studies concerning the mechanism were performed by Kende.[187] A detailed mechanism, which is based on these findings, described by Hultin (Scheme 91).[189]



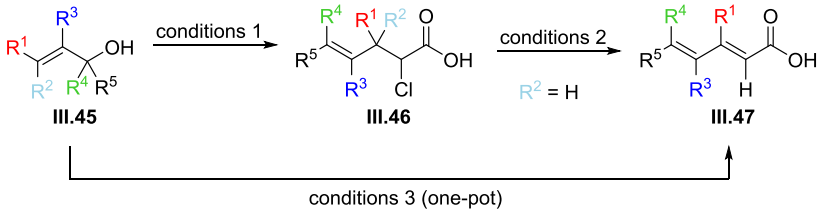
Scheme 91 Mechanism of the elimination-addition reaction of **III.20** using potassium phenolates **III.37**.

The previous studies continued at this point. By using allyl alcohol (**III.41**) the reaction did not stop at the 1,2-dichlorovinyl ether **III.42**, but underwent a subsequent Claisen rearrangement via a 6-membered transition state according to the Zimmerman-Traxler model. The resulting α-halogenated acid chloride **III.43** was finally hydrolyzed during the work-up (Scheme 92).



Scheme 92 General synthesis of 2-chloropent-4-enoic acid (**III.44**).

In this project, we envisaged to investigate a general methodology for the Claisen rearrangement of 1,2-dichlorovinyl ethers toward α-chloro-4-enoic acids (**III.46**) (Scheme 93). This approach was also extended by the possibility to generate 2,4-dienoic acids (**III.47**) via formal HCl elimination of the α-chloro-4-enoic acids (**III.46**). In addition, the development of a one-pot protocol for the preparation of the dienes should be established.

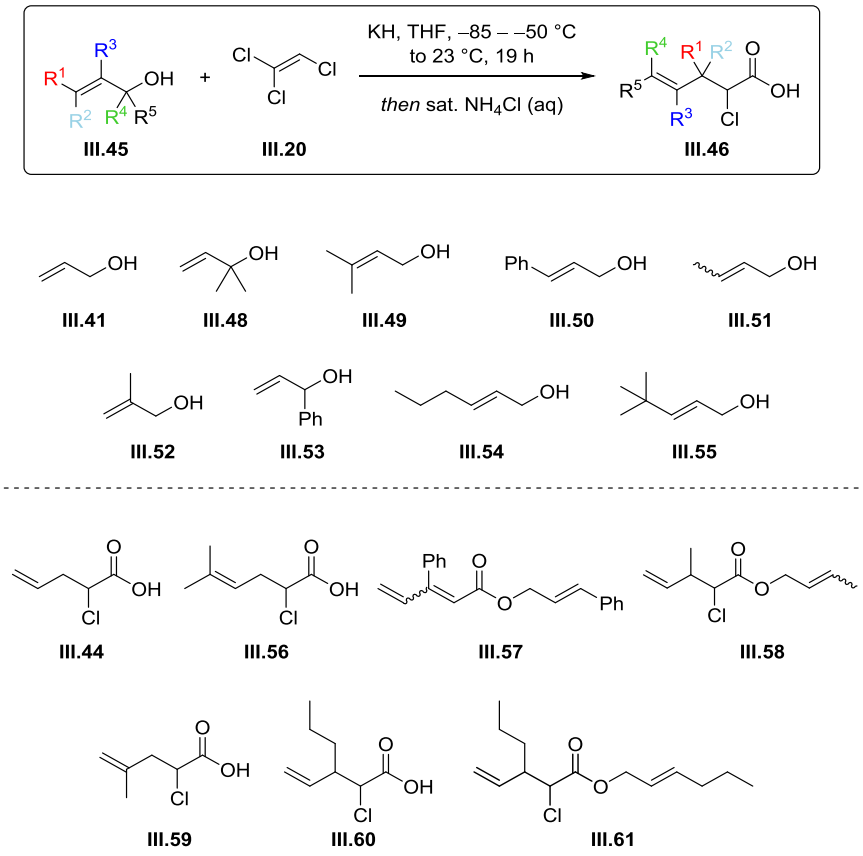


Scheme 93 Envisaged reaction pathway for the synthesis of α-chlorinated 4-pentenoic acids (**III.46**) and 2,4-dienoic acids (**III.47**).

8.1 Progress toward α-Chloro-4-enoic Acids

Due to the previous promising studies, the first intention was to evaluate, if the conditions for the preparation of 2-chloropent-4-enoic acids (**III.46**) tolerate various substitution patterns of the allylic alcohols (**III.45**). Therefore, several substrates were treated with KH (2.4 equiv) at low temperatures followed by the addition of TCE (**III.20**, 1.2 equiv) (Scheme 94). The reaction mixture was allowed to warm to 23 °C and was hydrolyzed with saturated aqueous NH_4Cl solution. The crude ^1H NMR spectra of all reactions looked quite promising. Unfortunately, the crude reaction products could not be purified by flash column chromatography on silica gel due to decomposition. We therefore tested a variety of purification methods, such as recrystallization, acid/base extraction, reverse-phase flash column chromatography and flash column chromatography on Florisil®. However, all purification approaches were met with failure. For this reason, the structure verification of the obtained products was only possible by NMR spectroscopy of the crude reaction mixture or subsequent elimination of the chloride. Nonetheless, several products could be identified: **III.44**, **III.56**, **III.57**, **III.58**, **III.59**, **III.60** and **III.61**. Interestingly, cinnamyl alcohol (**III.50**) and crotyl alcohol (**III.51**) afforded cinnamyl ester **III.59** and crotyl ester **III.58** instead of the corresponding acids. *Trans*-2-hexenol (**III.54**) gave a mixture of acid **III.59** and the corresponding hexenol ester **III.60**. Despite the drawback

concerning the purification we were able to see that the reaction in principal tolerates substituents on all positions of the allyl chain.



Scheme 94 Claisen rearrangement of various allylic alcohols.

To show an example of a product analysis, the assigned ^{1}H and ^{13}C NMR spectra of the crude diastereomeric mixture of acid **III.60** and its corresponding ester **III.61** are depicted in Figure 16. The assignment of the peaks was carried out by 2D NMR spectra. The ^{13}C NMR signal at 174 ppm refers clearly to the carbonyl group of **III.60** and the one at 169 ppm to the the carbonyl group of ester **III.61**. In the ^{1}H NMR spectrum, the doublets of 2 and 13 belong to the C*H*Cl moieties of the *anti*-diastereomer of both **III.60** and ester **III.61**. 2* and 13* belong to the corresponding *syn*-isomers.

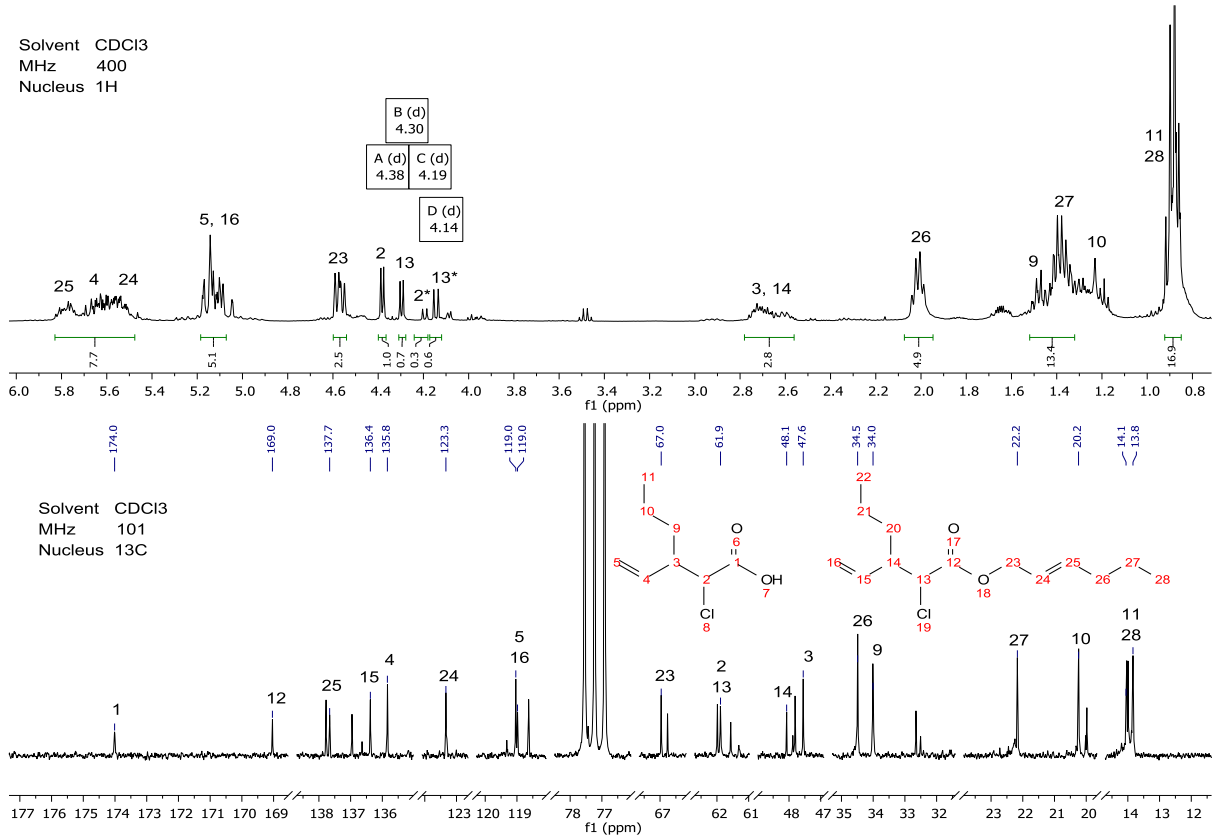
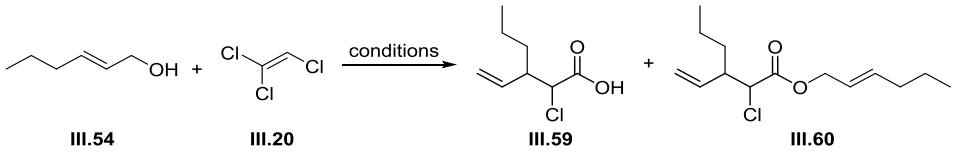


Figure 16 ^{1}H and ^{13}C NMR spectra of a diastereomeric mixture of acid **III.60** and the corresponding hexenol ester **III.61**. * indicates the *syn*-isomer.

During the screening of various allylic alcohols, we observed that for all substrates, except for **III.41**, large amounts of remaining starting material were detected. A possible explanation for this might be the incomplete formation of the enol ether. Therefore, we decided to focus on one substrate and try to optimize the reaction conditions. The selected substrate was *trans*-2-hexen-1-ol (**III.54**) and different addition orders as well as various substrate ratios were screened (Table 33). However, the results were only moderate. The best d.r. and overall yield, determined by ^{1}H NMR, was afforded in entry 1. An excess of TCE (**III.20**) decreased both the yield and the d.r. significantly (entry 2). With an excess of **III.54** (entry 4), only ester **III.60** could be identified.

Table 33 Screening of conditions for the Claisen rearrangement with *trans*-2-hexen-1-ol (**III.54**) as substrate.



III.54 **III.20** **III.59** **III.60**

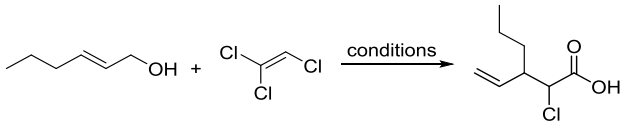
entry	conditions[a]	comment	result[b],[c]
1	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to 23 °C		**III.59** (34%), d.r. = 4.3 : 1 **III.60** (26%), d.r. = 1.4 : 1
2	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to 23 °C	ratio **III.54** : KH : **III.20** = 1 : 2.4 : 2	**III.59** (8%), d.r. = 1.4 : 1 **III.60** (9%), d.r. = 0.9 : 1
3	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to 23 °C		**III.59** (15%), d.r. = 1.2 : 1 **III.60** (13%), d.r. = 1 : 1
4	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to 23 °C	ratio **III.54** : KH : **III.20** = 3 : 2.4 : 1.2	**III.60** (39%), d.r. = 1 : 1
5	KH, **III.54**, 23 °C, *then* **III.20**, –78 °C to 23 °C		**III.59** (13%) **III.60** (9%), d.r. = 1.2 : 1
6	KH, **III.20**, 23 °C, *then* mixture added to **III.20**, 0 °C	ratio **III.54** : KH : **III.20** = 1 : 1 : 1	**III.60** (30%)

[a] ratio **III.54** : KH : **III.20** = 1 : 2.4 : 1.2 unless otherwise noted; [b] the yield was determined by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz; mesitylene as internal standard); [c] d.r. = *anti* : *syn*.

Since Tellier, who has published similar reactions,[180,181,182,190] quenched the enol ether with aqueous H_2SO_4 instead of saturated aqueous NH_4Cl, we tested his procedure for our reactions (Table 34). Surprisingly, the d.r. of **III.60** improved significantly (up to 99:1 in entries 3 and 7). Furthermore **III.60** was obtained exclusively, even though the yield was still quite low. Longer

reaction time at −27 °C (entries 4, 5, 6, 7, 8) or different addition orders of alkoxide and TCE (**III.20**) (entries 1 and 2) did not make any difference. The same result was provided by less equivalents of H_2SO_4 (entriy 7) as well as varied ratios of allyl alcohol (**III.54**) and TCE (**III.20**) (entries 5 and 6). Another test was to add methanol (entry 8) or hexafluoro-2-propanol (entry 9) to generate the corresponding ester directly when the Claisen rearrangement takes place, but only **III.54** and traces of **III.61** were observed.

Table 34 Screening of conditions for the Claisen rearrangement with **III.54**.



III.54 **III.20** **III.60**

entry	conditions[a]	comment	result[b],[c]
1	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C, *then* H_2SO_4 (10%), 23 °C		**III.60** (13%), d.r. = 19 : 1
2	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, −78 °C to −27 °C, *then* H_2SO_4 (10%), 23 °C		**III.60** (14%), d.r. = 13.3 : 1
3	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 1 : <u>4</u> : 1.2 : 1.2	**III.60** (10%), d.r. = 99 : 1
4	1) KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 1.5 h at −27 °C, *then* H_2SO_4 (10%), 23 °C		**III.60** (25%), d.r. = 15.7 : 1
5	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 45 min at −27 °C,	**III.54** : KH : **III.20** : H_2SO_4 = <u>1.8</u> : 2.4 : 1.2 : 1.2	**III.60** (28%), d.r. = 15.7 : 1

	then H_2SO_4 (10%), 23 °C		
6	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 45 min at −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 2.4 : 2.4 : 1.2 : 1.2	**III.60** (37%), d.r. = 13.3 : 1
7	1) KH, **III.54**, 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 50 min at −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 1 : 2.4 : 1.2 : 0.55	**III.60** (26%), d.r. = 99 : 1
8	KH, **III.54**, 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 50 min at −27 °C, *then* MeOH, 23 °C	3 equiv of MeOH	**III.54** and traces of **III.20**
9	KH, **III.54**, 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 50 min at −27 °C, *then* HFIP, 23 °C	3 equiv of HFIP	**III.54** and traces of **III.20**

[a] ratio **III.54** : KH : **III.20** : H_2SO_4 = 1 : 2.4 : 1.2 : 1.2 unless otherwise noted; [b] the yield was determined by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz; mesitylene as internal standard); [c] d.r. = *anti* : *syn*.

Even though the obtained d.r. was now excellent, the yield of the reaction remained low and large amounts of remaining starting material were still observed after the work-up. Thus, we performed a ^{1}H NMR experiment, to examine the dependence of the formation of the enol ether on the reaction time (Figure 17). The ^{1}H NMR spectra were measured every 10 °C, beginning at −80 °C and increasing the temperature every 15 min until reaching −30 °C. Since we assumed the enol ether formation at around −30 °C, the temperature was held there for 2 h and every 15 min a ^{1}H NMR spectrum was measured. Afterwards the reaction was gradually warmed to −10 °C while monitored by ^{1}H NMR as well. As expected, the formation of the enol ether started at −30 °C (singlet at 5.8 ppm). The peak increased during the first 45 min (from −30 ° (1) to −30 ° (4)) and remained rather constant. The conclusion of this observation is that the formation of the enol ether reaches an equilibrium at −30 °C, which could most likely be shifted to the product side by rising the temperature. Unfortunately it is not possible to warm

the reaction to considerably higher temperatures, since the Claisen rearrangement is taking place between −10 °C and 0 °C. The product of the Claisen rearrangement, an acid chloride, reacts rapidly with the present alkoxide to form an ester. Thereby, the alkoxide is removed from the equilibrium of the enol ether formation.

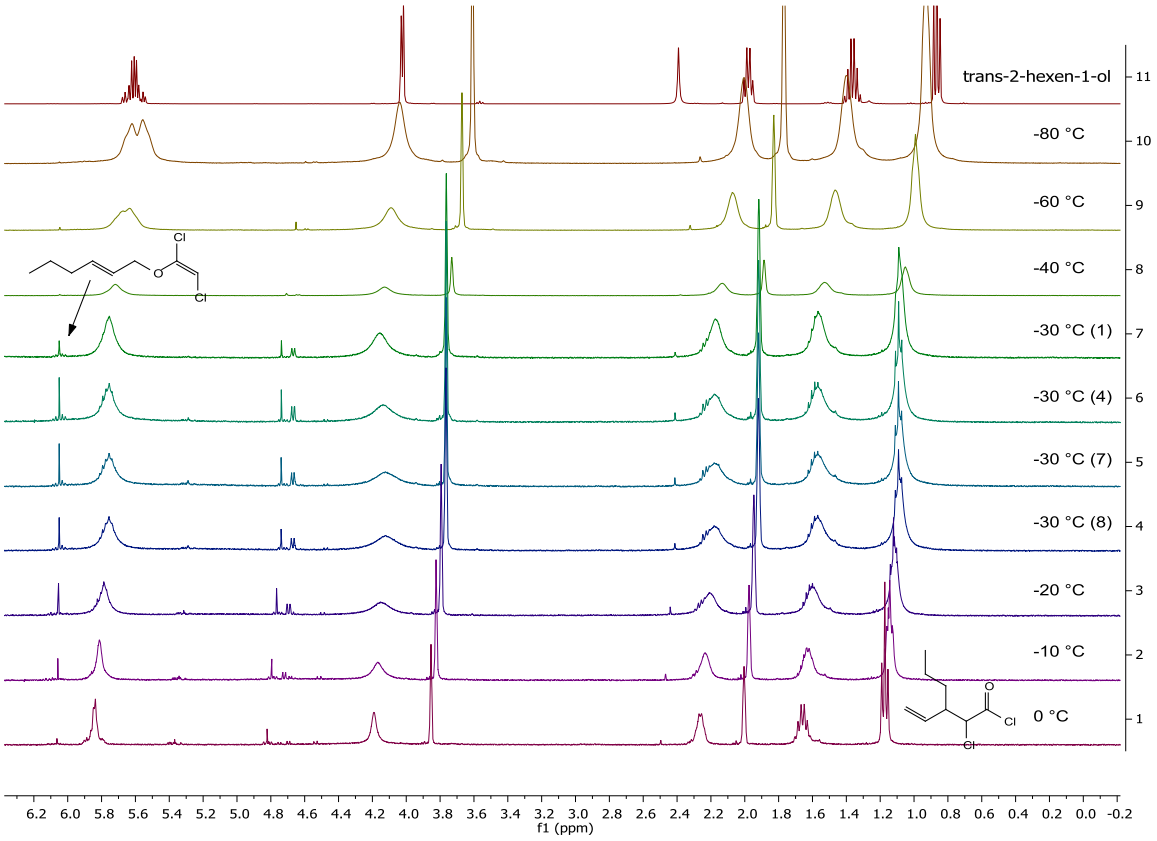
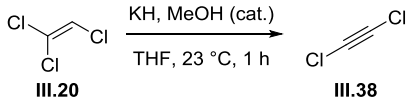


Figure 17 ^{1}H NMR study of the Claisen rearrangement of *trans*-2-hexen-1-ol (**III.54**) (400 MHz, THF-d_8).

A different strategy to improve the reaction was to prepare dichloroacetylene (DCA, **III.38**) directly instead of generating it in situ. Seminal studies were published about the dehydrochlorination of TCE (**III.20**).[188] If **III.20** is treated with a strong base, β-elimination leads to the formation of DCA (**III.38**).[191] A procedure of 1961 reports the passage of a gaseous mixture of **III.20** in diethyl ether through pyrex tubes, which contain a potassium hydroxide/calcium oxide mixture.[192] Another synthesis of **III.38** was carried out via phase-transfer catalysis (PTC).[191d,193] While Kende reported the use of LHMDS for the deprotonation of **III.38**,[194] KH and a catalytic amount of methanol was used by Greene for this transformation (Scheme 95).[191b]

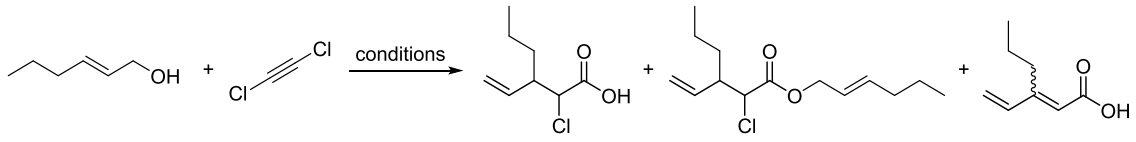
A solution of **III.38** in diethyl ether proved to be a practical method for the handling of this reagent, since a rather stable diethyl ether-DCA (**III.38**) complex is formed. Pure **III.38** is a highly explosive and toxic reagent.[188,195]



Scheme 95 Preparation of dichloroacetylene (DCA) (**III.38**).

Utilizing DCA (**III.38**), the formation of the enol ether and the subsequent Claisen rearrangement was performed with various ratios of **III.54** : KH : **III.38** (Table 35). However, the replacement of **III.20** by **III.38** did not result in any difference. **III.59** and **III.60** were obtained in the same low to moderate yields as before. With *t*-BuOK (entry 6) only ester **III.60** was observed in low yield. In another attempt, **III.54** was added at 0 °C to a mixture of KH, methanol and **III.38**, but only a diastereomeric mixture of dienes **III.61a** and **III.61b** was obtained in 33% yield (entry 8). A crystal structure could be obtained of *Z*-isomer **III.62b**, which confirmed the formation of the dienes (Figure 18).

Table 35 Screening for conditions of the Claisen rearrangement with DCA (**III.38**).



entry	conditions	comment	result[a],[b]
1	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 1 : 1.1 : 2	**III.60** (34%), d.r. = 10 : 1 **III.61** (12%), d.r. = 1.5 : 1
2	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 1 : 1.1 : 3	**III.60** (30%)
3	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 1 : 0.1 : 3	**III.54** and traces of **III.61**

4	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 3 : 1.5 : 1	**III.61** (56%), d.r. = 1 : 1
5	KH, **III.54**, 23 °C, *then* **III.38**, 23 °C	ratio **III.54** : KH : **III.38** = 2 : 2 : 1	**III.61** (45%), d.r. = 1.1 : 1 **III.62** (18%), d.r. = 1 : 1.4[c]
6	*t*-BuOK, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : *t*-BuOK : **III.38** = 1.3 : 1 : 1.3	**III.61** (22%), d.r. = 1.3 : 1
7	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 2 : 2 : 1	**III.60** (11%), d.r. = 6.14 : 1 **III.61** (8%), d.r. = 1 : 1.5 **III.62** (20%), d.r. = 1 : 1[c]
8	KH, MeOH, 23 °C, *then* **III.38**, 0 °C, *then* **III.54**, 0 °C (addition over 1.5 h)	ratio **III.54** : KH : **III.38** : MeOH = 1 : 3 : 1 : 2	**III.62** (33%), d.r. = 1 : 1.3[c]

[a] the yield was determined by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz; mesitylene as internal standard); [b] d.r. = *anti* : *syn*; [c] d.r. = *E* : *Z*.

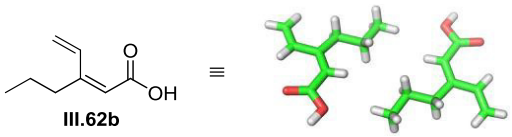


Figure 18 X-ray structur of *Z*-diene **III.62b**.

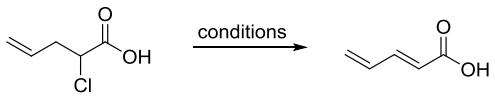
8.2 Progress toward 2,4-Dienoic Acids

At this point, the screening for the optimal conditions for the enol ether formation and subsequent Claisen rearrangement were abandoned. Instead, we focused on the formation of the 2,4-dienoic acids. This project was initially started to verify the structures of the α-chloro-4-enoic acids, since these were difficult to isolate in pure form. However, we then began to investigate this methodology further, also with the goal to develop a one-pot procedure based on the allylic alcohols.

For the initial screening, 2-chloropent-4-enoic acid (**III.44**) was used, due to the fact that its formation proceeded rather smoothly. Various bases, such as *t*-BuOK, DBU, KOTMS and NaOH were tested in combination with several solvents (Table 36). The best result was obtained for *t*-BuOK in *t*-BuOH (entry 1). Only product **III.63** was observed in the crude ^{1}H NMR spectrum, but it turned out that **III.63** partially decomposed (polymerization) during flash column chromatography on silica gel or Florisil®. Extraction via acid-base treatment failed as well. This observation is however not astonishing, since such diens tend to polymerize very easily. The commercially available (*E*)-penta-2,4-dienoic acid (**III.63**), for instance, contains hydroquinone as stabilizer to prevent polymerization.[196] For this reason, the conversion of the reactions was only monitored by ^{1}H NMR spectroscopy.

Since the conditions of entry 1 seemed to be most promising, they were used for the subsequent screening.

Table 36 Screening of various bases for diene synthesis.



III.44 **III.63**

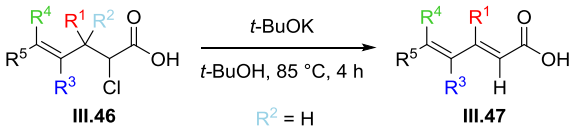
entry	base	conditions	result
1	*t*-BuOK (3.5 equiv)	*t*-BuOH, 85 °C, 5 h	**III.63**
2	*t*-BuOK (3.5 equiv)	*t*-BuOH, 50 °C, 4 h	**III.63**+ traces of **45**
3	DBU (3.5 equiv)	THF, 65 °C, 4 h	**III.44**
4	KOTMS (3.5 equiv)	THF, 85 °C, 4.5 h	**III.63** : **III.44** = 2 : 1[a]
5	*t*-BuOK (2.1 equiv)	*t*-BuOH, 85 °C, 4.5 h	**III.63** : **III.44** = 3 : 1[a]
6	*t*-BuOK (ca. 10 equiv)	*t*-BuOH, 23 °C, 4.5 h	**III.63** + traces of **III.44**
7	NaOH (3.5 equiv)	*i*-PrOH, 85 °C, 5 h	**III.63** : **III.44** = 6.7 : 1[a]

[a] ratio determined by ^{1}H NMR spectroscopy.

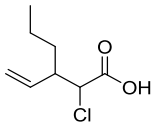
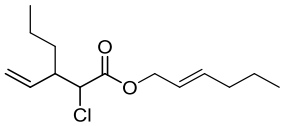
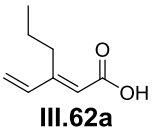
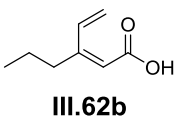
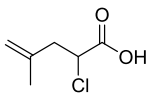
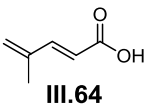
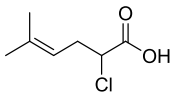
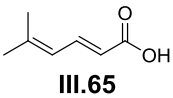
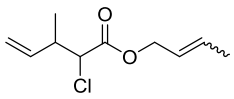
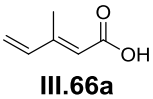
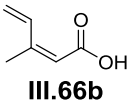
Using the optimized elimination conditions, the products of the Claisen rearrangement were converted into the corresponding dienes (Table 37). However, the obtained dienes often decomposed upon purification by flash column chromatography on silica gel, but mass spectroscopy and ^{1}H NMR spectroscopy of the crude reaction mixture allowed the determination of their structure. The reaction of a mixture of **III.60** and **III.61** (entry 1)

afforded the double bonds isomers **III.62a** and **III.62b** with a d.r. of = 1 : 3.5 after column chromatography. Acid **III.64** (entry 2) was isolated in 60% yield and acid **III.65** (entry 3) in 18%, both after column chromatography. In entry 4, the ester **III.58** must have been cleaved by the basic conditions to afford both isomers **III.66a** and **III.66b** as a mixture of double bond isomers (d.r. = 3 : 2).

Table 37 Elimination reaction of various α-chloro-4-enoic acids (**III.46**).



III.46 III.47

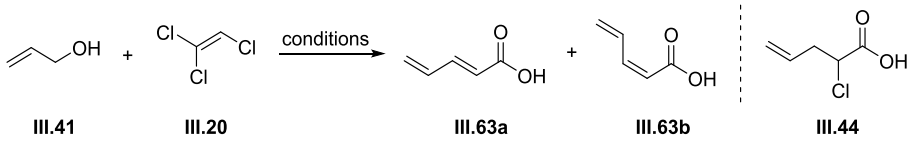
entry	substrate	product	result[a],[b]
1	 III.60  III.61	 III.62a  III.62b	d.r. = 1 : 3.5
2	 III.59	 III.64	60%
3	 III.56	 III.65	18%
4	 III.58	 III.66a  III.66b	d.r. = 3 : 2

[a] d.r. = *E* : *Z* was determined by ^{1}H NMR spectroscopy; [b] yield refers to isolated yield.

Since the preparation of 2,4-dienoic acids **III.47** over two steps seemed to be promising, conditions for a one-pot protocol were screened (Table 38). For the first part of the reaction, the Claisen rearrangement, we used our standard conditions with TCE (**III.20**). For the second part, the elimination, various reaction parameter like temperature (entry 1), time (entries 3 and 4) and equivalents of *t*-BuOK (entries 2, 4, 5 and 6) were tested. The ratio of **III.63a** : **III.44** was determined by 1H NMR spectroscopy. The best ratio of **III.63a** : **III.44** for the *t*-BuOH/*t*-BuOK conditions was obtained by heating the mixture with to 85 °C for 5 h (entry

2). Traces of *Z*-diene **III.63b** were determined for all reactions with *t*-BuOH/*t*-BuOK (entries 1–4 and 6). However, in the end we found out that using NaOH/*i*-PrOH was superior to all other tested conditions (entry 7). The ratio of **III.63a** : **III.44** is 11.5 : 1 and the d.r. of **III.63a** : **III.63b** is 9 : 1. Therefore the conditions of entry 7 were used for the following one-pot reactions.

Table 38 Screening of conditions for the one-pot reaction.



III.41 III.20 III.63a III.63b III.44

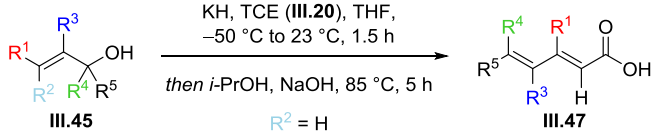
entry	conditions	ratio of III.63a : III.44[a]
1	1) KH, THF, −50 °C to 23 °C, 2.5 h 2) *t*-BuOK (3.5 equiv), 60 °C, 4.5 h	2.3 : 1; traces of **III.63b**
2	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (3.5 equiv), 80 °C, 4 h	5.3 : 1; traces of **III.63b**
3	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (3.5 equiv), 85 °C, 15 h	3.5 : 1; traces of **III.63b**
4	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (4 equiv), 85 °C, 15 h	2.7 : 1
5	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (2 equiv), 85 °C, 5 h	2.3 : 1; traces of **III.63b**
6	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (1.5 equiv), 85 °C, 5 h	3 : 1; traces of **III.63b**
7	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *i*-PrOH, NaOH (3.5 equiv), 85 °C, 5.5 h	ratio **III.63a** : **III.44** = 11.5 : 1 d.r. **III.63a** : **III.63b** = 9 : 1

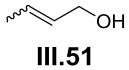
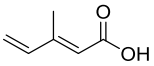
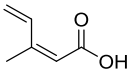
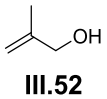
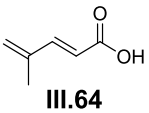
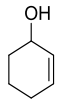
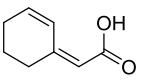
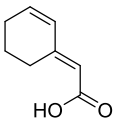
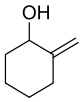
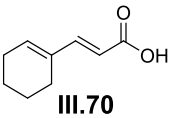
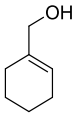
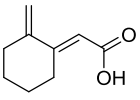
[a] ratios determined by ^{1}H NMR spectroscopy.

In Table 39, the established one-pot protocol was tested on a few substrates. In entry 1 an isomeric mixture of crotyl alcohol (**III.51**) was used. The diastereomers **III.66a** and **III.66b**

were isolated with a d.r. of 1 : 0.77. Diene **III.64** (entry 2) was isolated in quantitative yield without the need of purification. Racemic cyclohexeneol (**III.67**), used in entry 3, was converted into **III.68a** and **III.68b** (d.r. = 1 : 1). In entry 4, only 4% of diene **III.70** were obtained together with remaining allyl alcohol **III.69**. The product of entry 5 could be obtained, but no yield was determined.

Table 39 One-pot reaction.

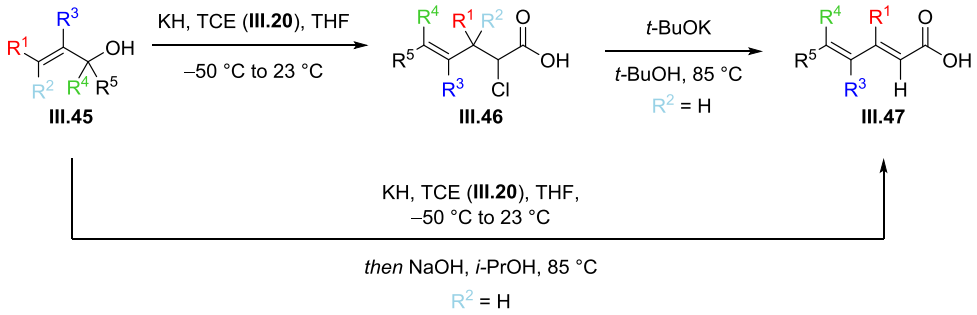


entry	substrate	product		result[a],[b]
1	 **III.51**	 **III.66a**	 **III.66b**	d.r. = 1 : 0.77
2	 **III.52**	 **III.64**		**III.64** (99%)
3	 **III.67**	 **III.68a**	 **III.68b**	d.r. = 1 : 1
4	 **III.69**	 **III.70**		**III.70** (4%)
5	 **III.71**	 **III.72**		**III.72** (n. d.)

[a] yields refer to isolated yields; [b] d.r. = *E* : *Z* determined by ^{1}H NMR spectroscopy.

9 Conclusion and Outlook

In summary, the Claisen rearrangement of allyl chlorovinyl ethers has been investigated in this thesis. We were able to obtain a variety of rearranged products and subsequently converted them to the corresponding 2,4-dienoic acids (**III.47**). A one-pot protocol for this reaction sequence, starting from readily available allyl alcohols (**III.45**), was established as well (Scheme 96). Using a modified work-up procedure, the diastereomeric ratio of the α-chlorinated 4-pentenoic acids (**III.46**) could be increased to 99 : 1 (*anti* : *syn*).



Scheme 96 Synthesis of α-chlorinated 4-pentenoic acids (**III.46**) and 2,4-dienoic acids (**III.47**).

However, since both carboxylic acid derivatives were very sensitive toward purification, their isolation and identification proved very complicated. In addition, the in situ formation of the 1,2-dichlorovinyl ether was challenging as it proceeded slowly at −30 °C, but did not complete until −10 °C whereupon the Claisen rearrangement took place. For this reason, the yields of the rearrangement products were relatively low, and sometimes the α-chlorinated esters were isolated instead of the acids.

Future experiments have to be dedicated to find an appropriate way to efficiently prepare the 1,2-dichlorovinyl ethers and to purify the α-chlorinated acids and the 2,4-dienoic acids. With regard to the 2,4-dienoic acids, allyl alcohols with substituents at the C1-position would be beneficial, as such substitution prevents polymerization reactions. However, substrates such as 3-methylbut-2-en-1-ol (**III.49**), containing two substituents at the C3-position, would be ideal for the α-chlorinated acids. The two substituents would generate a quaternary center at the β-position of the Claisen rearrangement product and thus prohibit the elimination of chloride.

CHAPTER IV

EXPERIMENTAL PART

10 Experimental Part

10.1 Materials and Methods

General Experimental Details

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above room temperature were conducted in a heated oil or water bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminium plates precoated with silica gel (0.25 mm, 60 Å pore size, Merck) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$), ceric ammonium molybdate solution (CAM) or *p*-anisaldehyde solution (ANIS) and were developed by heating with a heat gun. Flash 1 column chromatography was performed as described by Still et al.,[197] employing silica gel (60 Å, 40–63 μm, Merck KGaA). Flash-column chromatography on silica gel using triethylamine pretreated silica gel was performed by preparing the silica gel slurry with triethylamine (1% v/v in corresponding eluent mixture) and flushing the column with the eluent prior to loading the compound on the column. The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

Materials

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under N_2 atmosphere from Na/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA) and Hünig's base (DIPEA) were distilled under nitrogen atmosphere from CaH_2 prior to use. Dimethyl sulfoxide (DMSO), acetonitrile (MeCN), benzene, toluene, *N*,*N*-dimethylformamide (DMF), acetone, *n*-hexane, 1,4-dioxane,chlorobenzene, trifluorotoluene, 1,2-dichloroethane (DCE), Methyl *tert*-butyl ether (MTBE), Cyclopentyl methyl ether (CPME), dimethoxyethane (DME) and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents and used as received. Potassium hydride (KH) (purchased as a 30 wt% dispersion in mineral oil from Sigma-Aldrich) was washed three times with dry *n*-hexane

and dried under vacuum prior to use. All other reagents and solvents were purchased from chemical suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR, Carbolution) and were used as received. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three titrations).[198]

NMR spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbeTM, *Bruker* AXR300, *Varian* VXR400 S, *Bruker* AMX600 or Bruker Avance HD 800. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, methanol-d3: δ 4.78, acetone-d5: δ 2.05, $CDHCl_2$: δ 5.32). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_3OD: δ 49.00, acetone-d6: δ 29.84, CD_2Cl_2: δ 54.00). ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. Coupling constants *J* are reported in Hz. All raw fid files were processed and the spectra analyzed using the program *MestReNOVA 9.1* from *Mestrelab Research S. L.*

Mass spectroscopy

All mass spectra were measured by the analytic section of the Department of Chemistry, Ludwig-Maximilians-Universität München. Mass spectra were recorded on the following spectrometers (ionization mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from Thermo

Finnigan GmbH. Mass spectra were recorded in high-resolution. The used method is reported at the relevant section of the experimental section.

IR spectroscopy

IR spectra were recorded on a PerkinElmer Spectrum BX II FT-IR system. If required, substances were dissolved in CH_2Cl_2 prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (*vs* = very stong, *s* = strong, *m* = medium, *w* = weak).

HPLC

HPLC was performed with HPLC grade solvents. All solvents were degassed by a fluoroethylene membrane prior to use.

Chiral HPLC spectra were recorded on a high performance liquid chromatography (HPLC) system from Shimadzu 20A series (DGU-20A3R degasser, LC-20AD Binary Pump VL, SIL-20AHT autosampler, FCV-14AH thermostated column compartment, SPD-M20A IVDD diode array detector), which was computer controlled through Shimadzu LabSolutions Software (Version 5.42 SP5). Enantiomeric excess (*ee*) was calculated by using the following equation; m_1 refers to the integral of the major peak and m_2 to the integral of the minor peak:

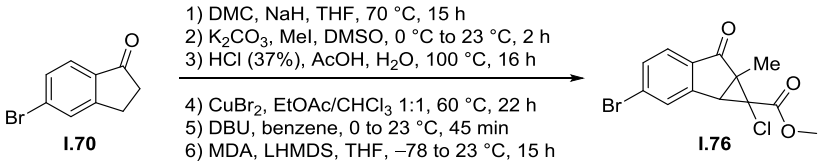
$$ee = \frac{|m_1 - m_2|}{m_1 + m_2} \cdot 100\%$$

10.2 Experimental Procedures

10.2.1 Salimabromide

10.2.1.1 First Generation Approach

5-Bromo-2-methyl-2,3-dihydro-1*H*-inden-1-one (I.76):



To a suspension of sodium hydride (60% dispersion in mineral oil, 19.9 g, 497 mmol, 2.00 equiv) and dimethyl carbonate (39.9 mL, 474 mmol, 2.00 equiv) in tetrahydrofuran (474 mL) in a 3-necked 1 liter round bottom flask fitted with a reflux condenser, dropping funnel and thermometer was added 5-bromo-1-indanone (**I.70**) (50.0 g, 237 mmol, 1 equiv) in tetrahydrofuran (677 mL) at 0 °C over 45 min. The dark brown reaction mixture was stirred at 0 °C for 30 min, warmed very slowly to 23 °C and heated carefully to 70 °C for 15 h. Afterwards, it was cooled to 0 °C and diluted with saturated aqueous ammonium chloride solution (200 mL), aqueous hydrogen chloride solution (2 M; 200 mL) and diethyl ether (300 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 400 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **I.71** was afforded as a dark brown solid and was used without additional purification for the next step.

To crude **I.71** in dry dimethyl sulfoxide (240 mL) was added potassium carbonate (65.5 g, 474 mmol, 2.00 equiv) portionwise at 0 °C. After dropwise addition of methyl iodide (29.5 mL, 474 mmol, 2.00 equiv) the dark green slurry was stirred at 23 °C for 2 h. The excess methyl iodide was removed by distillation (23 °C, 50 mbar). The reaction mixture was cooled to 0 °C, diluted with saturated aqueous ammonium chloride solution (100 mL), water (100 mL) and ethyl acetate (250 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 400 mL). The combined organic layers were washed with saturated aqueous sodium

chloride solution (300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **I.72** was afforded as a dark brown solid and was used without additional purification for the next step. An analytical pure sample of **I.72** was obtained by flash column chromatography on silica gel (9% ethyl acetate in hexanes).

Analytical data for I.72:

TLC (20% ethyl acetate in hexanes), R_f = 0.40 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 3.69 (s, 1H), 3.64 (s, 3H), 2.95 (d, *J* = 17.3 Hz, 1H), 1.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.1, 172.0, 154.2, 133.5, 131.6, 130.9, 129.8, 126.1, 56.1, 52.9, 39.6, 21.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*w*), 1742 (*s*), 1710 (*vs*), 1594 (*s*), 1579 (*m*), 1428 (*m*), 1317 (*m*), 1266 (*s*), 1200 (*s*), 1177 (*s*), 1095 (*m*), 1057 (*m*), 964 (*s*), 919 (*m*), 830 (*m*), 769 (*m*), 668 (*m*), 593 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{11}O_3{}^{81}Br$ $[M]^+$: 283.9866; found: 283.9875.

Crude **I.72** was dissolved in water (82 mL), glacial acetic acid (400 mL) and aqueous hydrogen chloride solution (37%, 125 mL, 924 mmol, 3.90 equiv). The reaction mixture was heated to 100 °C for 16 h. After cooling to 23 °C, the solution was diluted with dichloromethane (300 mL) and water (300 mL) and was carefully neutralized by portionwise addition of sodium bicarbonate (250 g) and aqueous sodium hydroxide solution (10%, 300 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 400 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **I.73** was afforded as a dark brown solid and was used without additional purification for the next step. An analytical pure sample of **I.73** was obtained by flash column chromatography on silica gel (2% ethyl acetate in hexanes).

Analytical data for I.73:

TLC (20% ethyl acetate in hexanes), R_f = 0.56 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 – 7.56 (m, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 3.37 (dd, *J* = 18.1, 8.8 Hz, 1H), 2.70 (dt, *J* = 12.1, 3.5 Hz, 2H), 1.29 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.2, 155.2, 135.3, 131.1, 130.1, 129.9, 125.3, 42.1, 34.7, 16.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2964 (*w*), 2930 (*w*), 1707 (*vs*), 1594 (*vs*), 1572 (*m*), 1412 (*m*), 1318 (*m*), 1265 (*m*), 1199 (*m*), 1055 (*m*), 963 (*s*), 882 (*m*) 858 (*m*), 825 (*m*), 764 (*m*), 676 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{10}H_9O^{81}Br$ $[M]^+$: 225.9811; found: 225.9814.

To crude indanone **I.73**, dissolved in ethyl acetate (1 L) and chloroform (1 L), was added copper(II) bromide (106 g, 474 mmol, 2.00 equiv). The green suspension was stirred with a KPG stirrer, while it was heated to 70 °C. After 22 h, it was cooled to 23 °C, filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **I.74** was used without additional purification for the next step. An analytical pure sample of **I.74** was obtained by flash column chromatography on silica gel (2% ethyl acetate in hexanes).

Analytical data for I.74:

TLC (20% ethyl acetate in hexanes), R_f = 0.57 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 3.77 (d, *J* = 18.3 Hz, 1H), 3.47 (d, *J* = 18.3 Hz, 1H), 1.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.2, 150.7, 132.1, 131.7, 131.4, 129.8, 127.0, 59.2, 46.1, 26.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1723 (*vs*), 1596 (*s*), 1575 (*w*), 1423 (*w*), 1320 (*m*), 1266 (*w*), 1210 (*w*), 1057 (*m*), 973 (*m*), 900 (*w*), 857 (*w*), 831 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{10}H_8O^{79}Br_2$ $[M]^+$: 301.8936; found: 301.8937.

To crude indanone **I.74** in benzene (474 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (106 mL, 711 mmol, 3.00 equiv) at 0 °C. After 5 min, the solution was warmed to 23 °C and was stirred for 45 min. The reaction mixture was diluted with saturated aqueous ammonium chloride solution (100 mL) and diethyl ether (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate

was concentrated (>200 mbar). The crude product **I.75** was afforded as a yellow-brown oil and was used immediately without additional purification for the next step. *Note: Indenones undergo facile polymerizations and should therefore be used immediately after preparation.*

Note: For safety reasons the cyclopropanation was carried out in two parallel batches. The crude material of both batches was subsequently combined and purified together.

To a stirred solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 137 mL, 137 mmol, 1.15 equiv) in tetrahydrofuran (119 mL) in a 3-necked 2 liter round bottom flask fitted with a reflux condenser, dropping funnel and thermometer, was added methyl dichloroacetate (12.9 mL, 125 mmol, 1.05 equiv) over 30 min at −78 °C. After stirring for 105 min, a solution of crude **I.75** in tetrahydrofuran (238 mL) was added over 1.5 h and after the addition, the reaction mixture was allowed to warm slowly to 23 °C. After 16 h, the mixture was cooled to 0 °C and diluted with saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (300 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2 to 3.2% ethyl acetate in hexanes) to obtain **I.76** (38.9 g, 50% over 6 steps, inconsequential mixture of diastereomers) as a yellow solid.

Analytical data for I.76:

Note: Traces of the minor diastereomer are visible in the ^{1}H and ^{13}C NMR spectra, but solely the resonances of the major diastereomer are listed below.

TLC (20% ethyl acetate in hexanes), R_f = 0.47 (UV, $KMnO_4$).

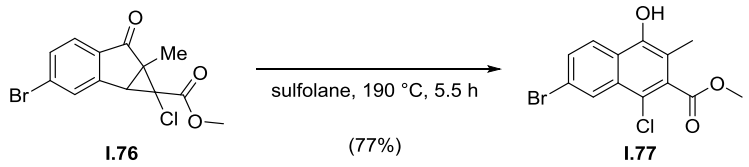
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.54 (s, 2H), 3.86 (s, 3H), 3.71 (s, 1H), 1.51 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 197.3, 165.9, 149.4, 134.5, 132.2, 129.9, 129.8, 125.3, 64.9, 53.9, 42.8, 37.3, 9.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1717 (*vs*), 1597 (*s*), 1579 (*m*), 1435 (*m*), 1356 (*w*), 1283 (*m*), 1260 (*s*), 1237 (*s*), 1206 (*m*), 1162 (*m*), 1107 (*w*), 1055 (*m*), 988 (*w*), 952 (*m*), 938 (*m*), 889 (*m*), 836 (*m*), 788 (*w*), 777 (*w*), 738 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{10}O_3{}^{79}Br^{35}Cl$ $[M]^+$: 327.9496; found: 327.9505.

Methyl 7-bromo-1-chloro-4-hydroxy-3-methyl-2-naphthoate (I.77):



I.76 **I.77**

Note: The reaction was carried out in two parallel batches. The crude material of both batches was subsequently combined and purified together.

A solution of **I.76** (8.90 g, 27.0 mmol, 1 equiv) in sulfolane (54 mL) was heated to 190 °C for 5.5 h and then cooled to 23 °C. The reaction mixture was diluted with diethyl ether (200 mL) and water (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed successively with saturated aqueous sodium chloride solution (200 mL) and water (3 × 300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to provide **I.77** (13.8 g, 77%) as a brown solid.

Analytical data for I.77:

TLC (20% ethyl acetate in hexanes), R_f = 0.18 (UV, $KMnO_4$).

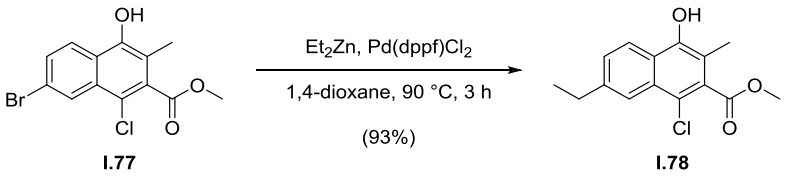
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.94 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 5.65 (s, 1H), 4.02 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.5, 148.4, 133.5, 130.6, 130.5, 126.8, 124.2, 123.8, 122.2, 118.9, 115.0, 53.2, 13.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3330 (*w*), 2951 (*w*), 1695 (*vs*), 1619 (*w*), 1583 (*m*), 1558 (*w*), 1439 (*s*), 1378 (*m*), 1361 (*m*), 1275 (*vs*), 1247 (*vs*), 1177 (*m*), 1111 (*m*), 1074 (*m*), 1053 (*m*), 962 (*m*), 927 (*s*), 874 (*m*), 863 (*m*), 823 (*vs*), 761 (*m*), 741 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{10}O_3{}^{79}Br^{35}Cl$ $[M]^+$: 327.9496; found: 327.9492.

Methyl 1-chloro-7-ethyl-4-hydroxy-3-methyl-2-naphthoate (I.78):



I.77 I.78

Note: The reaction setup has to be flame-dried very carefully, since otherwise the yield decreases significantly.

To [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (400 mg, 0.546 mmol, 0.0180 equiv) was added a solution of **I.77** (10.0 g, 30.3 mmol, 1 equiv) in 1,4-dioxane (25 mL). The red suspension was cooled to 0 °C and a freshly prepared solution of diethylzinc (1 M in toluene, 60.1 mL, 60.7 mmol, 2.00 equiv) was added very carefully over 30 min. After the addition, the dark red mixture was allowed to warm to 23 °C over 30 min and the beige suspension was then heated very carefully to 90 °C. After 3 h, it was cooled to 0 °C and methanol (20 mL) was added dropwise. Water (100 mL) and aqueous hydrochloric acid solution (2 M, 100 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to obtain **I.78** (7.82 g, 93%) as a red-brown oil.

Analytical data for I.78:

TLC (20% ethyl acetate in hexanes), R_f = 0.31 (UV, $KMnO_4$).

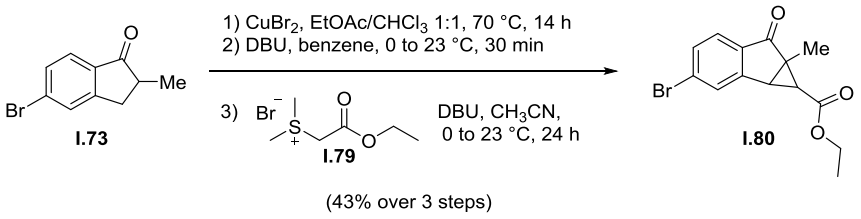
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.6 Hz, 1H), 7.97 (q, *J* = 0.9 Hz, 1H), 7.45 (dd, *J* = 8.7, 1.7 Hz, 1H), 5.37 (s, 1H), 4.03 (s, 3H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 1.63 (s, 1H), 1.36 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.6, 148.2, 143.7, 132.7, 130.0, 128.3, 123.9, 122.7, 121.6, 119.6, 113.1, 52.9, 29.3, 15.6, 13.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3475 (*w*), 2362 (*m*), 1715 (*s*), 1438 (*m*), 1387 (*m*), 1293 (*m*), 1239 (*vs*), 1053 (*m*), 668 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{15}O_3{}^{35}Cl$ $[M]^+$: 278.0704; found: 278.0699.

Ethyl 3-bromo-6a-methyl-6-oxo-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylate (I.80):



To indanone **I.73** (2.00 g, 8.89 mmol, 1 equiv), dissolved in ethyl acetate (39 mL) and chloroform (39 mL), was added copper(II) bromide (3.97 g, 17.8 mmol, 2.00 equiv). The green suspension was stirred vigorously, while it was heated to 70 °C. After 14 h, it was cooled to 23 °C, filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **I.74** was used without additional purification for the next step.

To crude indanone **I.74** in benzene (18 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (3.98 mL, 26.7 mmol, 3.00 equiv) at 0 °C. After 5 min, the solution was warmed to 23 °C and was stirred for 30 min. The reaction mixture was diluted with saturated aqueous ammonium chloride solution (30 mL) and diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **I.75** was afforded as a yellow-brown oil and was used without additional purification for the next step. *Note: Indenones undergo facile polymerizations and should therefore be used immediately after preparation.*

To a suspension of salt **I.79**[199] (2.04 g, 8.89 mmol, 1 equiv) in acetonitrile (11 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.59 mL, 10.7 mmol, 1.20 equiv) dropwise at 0 °C. After stirring for 1 h, a solution of the crude indenone **I.75** in acetonitrile (33 mL) was added over 30 min. The reaction mixture was stirred for 21 h during which the temperature warmed to 23 °C and was then diluted with aqueous hydrogen chloride solution (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with aqueous hydrogen chloride solution (2 M, 50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2 to 3% ethyl acetate in hexanes) to afford **I.80** (1.17 g, 43% over 3 steps) as an orange solid.

Analytical data for I.80:

TLC (20% ethyl acetate in hexanes), R_f = 0.57 (UV).

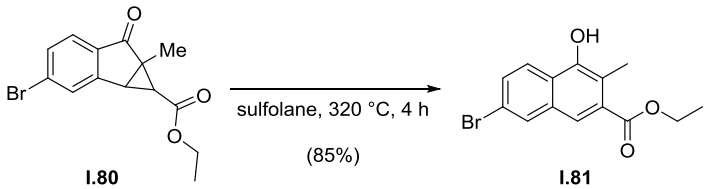
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.24 (d, *J* = 2.6 Hz, 1H), 2.22 (d, *J* = 2.8 Hz, 1H), 1.58 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.01, 167.04, 153.48, 131.78, 131.13, 129.58, 128.21, 126.30, 61.46, 47.52, 38.46, 31.87, 14.38, 8.28.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (*w*), 1716 (*vs*), 1598 (*m*), 1453 (*w*), 1383 (*w*), 1305 (*w*), 1268 (*w*), 1205 (*m*), 1178 (*m*), 1106 (*w*), 1056 (*w*), 965 (*w*), 875 (*w*), 785 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{13}O_3{}^{79}Br$ $[M]^+$: 308.0043; found: 308.0046.

Ethyl 7-bromo-4-hydroxy-3-methyl-2-naphthoate (I.81):



I.80 **I.81**

In a flask with reflux condenser was heated **I.80** (3.0 g, 9.7 mmol, 1 equiv) in sulfolane (97 mL) in a "Luftbad" (Figure 19) to 320 °C for 4 h. After cooling to 23 °C, the reaction mixture was diluted with water (100 mL) and diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with water (5 × 150 mL) and saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **I.81** (2.56 g, 85%) as an orange solid.

Analytical data for I.81:

TLC (20% ethyl acetate in hexanes), R_f = 0.23 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.8 Hz, 1H), 7.92 (s, 1H), 7.84 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 5.63 (s, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 2.53 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H).

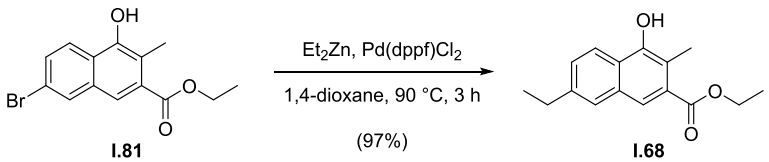
^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.1, 149.8, 132.7, 130.8, 130.6, 130.4, 124.3, 123.6, 122.5, 120.5, 116.4, 61.5, 14.5, 12.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3445 (*m*), 2980 (*w*), 2935 (*w*), 1696 (*s*), 1583 (*m*), 1567 (*m*), 1444 (*m*), 1372 (*s*), 1329 (*m*), 1275 (*vs*), 1224 (*vs*), 1211 (*vs*), 1111 (*m*), 1046 (*vs*), 985 (*m*), 907 (*m*), 818 (*m*), 777 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{13}O_3{}^{79}Br$ $[M]^+$: 308.0043; found: 308.0040.

Figure 19 Experimental set up for the synthesis of **I.81**. For safety reasons the whole experimental set up is assembled behind a blast shield.

Ethyl 7-ethyl-4-hydroxy-3-methyl-2-naphthoate (I.68):



Note: The reaction setup has to be flame-dried very carefully, since the yield otherwise decreases significantly.

To [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (107 mg, 0.146 mmol, 0.0180 equiv) was added a solution of **I.81** (2.50 g, 8.09 mmol, 1 equiv) in 1,4-dioxane (6.7 mL). The red suspension was cooled to 0 °C and diethylzinc solution (15wt% in toluene, 14.6 mL,

16.2 mmol, 2.00 equiv) was added dropwise. After stirring for 20 min, the beige suspension was heated to 90 °C for 3 h, cooled to 0 °C and carefully treated with methanol (8 mL). Water (20 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with aqueous hydrogen chloride solution (2 M, 20 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **I.68** (2.04, 97%) as an orange oil.

Analytical data for I.68:

TLC (20% ethyl acetate in hexanes), R_f = 0.32 (UV, CAM).

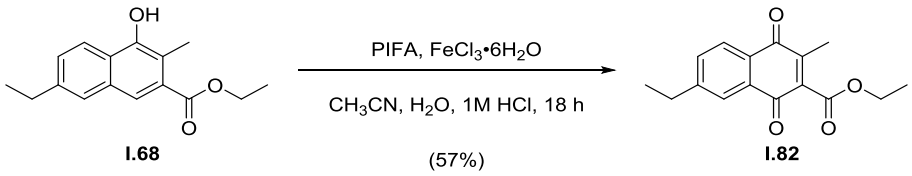
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.7 Hz, 1H), 7.97 (s, 1H), 7.61 (s, 1H), 7.41 (dd, *J* = 8.6, 1.7 Hz, 1H), 5.43 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.5, 149.6, 142.3, 132.1, 129.7, 128.8, 126.4, 124.4, 123.5, 121.3, 115.1, 61.1, 29.0, 15.4, 14.5, 12.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3452 (*w*), 2967 (*w*), 2932 (*w*), 1715 (*vs*), 1601 (*m*), 1572 (*w*), 1456 (*m*), 1395 (*m*), 1379 (*m*), 1290 (*s*), 1229 (*s*), 1210 (*s*), 1112 (*s*), 1094 (*s*), 1047 (*s*), 981 (*m*), 901 (*m*), 930 (*m*), 780 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{18}O_3$ $[M]^+$: 258.1250; found: 258.1247.

Ethyl 7-ethyl-3-methyl-1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (I.82):



To a solution of **I.68** (100 mg, 0.387 mmol, 1 equiv) in acetonitrile (11 mL) and water (6 mL) was added [bis(trifluoroacetoxy)iodo]benzene (250 mg, 0.581 mmol, 1.50 equiv) at 0 °C. The ice bath was removed after the addition and the reaction mixture was stirred for 2 h at 23 °C. After this time, a solution of iron(III) chloride hexahydrate (299 mg, 1.11 mmol, 2.86 equiv) in aqueous hydrochloric acid solution (1 M, 2.8 mL) was added. After 16 h, water (20 mL) and ethyl

acetate (20 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (4 to 5% ethyl acetate in hexanes) to obtain **I.82** (60.3 mg, 57%) as a yellow solid.

Analytical data for I.82:

TLC (20% ethyl acetate in hexanes), R_f = 0.42 (UV, CAM).

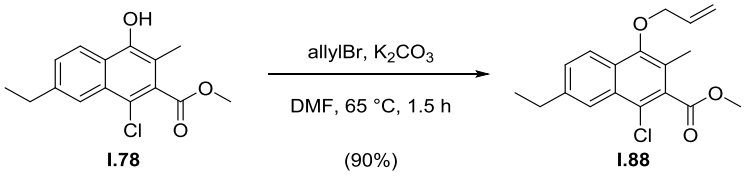
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.56 (dd, *J* = 7.9, 2.2 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.79 (q, *J* = 7.6 Hz, 2H), 2.17 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 184.8, 182.1, 164.8, 151.6, 143.9, 139.7, 133.9, 131.6, 129.8, 127.1, 125.8, 62.2, 29.3, 15.1, 14.4, 13.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2964 (*w*), 1732 (*m*), 1668 (*m*), 1659 (*m*), 1602 (*m*), 1372 (*s*), 1294 (*vs*), 1233 (*s*), 1203 (*m*), 1128 (*m*), 1103 (*m*), 1051 (*m*), 1017 (*m*), 970 (*m*), 958 (*m*), 853 (*w*), 778 (*w*), 771 (*m*), 734 (*m*), 722 (*m*), 657 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{16}O_4$ $[M]^+$: 272.1043; found: 272.1043.

Methyl 4-(allyloxy)-1-chloro-7-ethyl-3-methyl-2-naphthoate (I.88):



To a solution of **I.78** (100 mg, 0.359 mmol, 1 equiv) in dimethylformamide (1.2 mL) were successively added potassium carbonate (74.4 mg, 0.538 mmol, 1.50 equiv) and allyl bromide (34.2 µL, 47.7 mmol, 1.10 equiv) and the reaction mixture was heated to 65 °C. After 1.5 h, water (10 mL) and diethyl ether (15 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with aqueous hydrochloric acid solution (2 M, 30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column

chromatography on silica gel (5% ethyl acetate in hexanes) to yield **I.88** (103 mg, 90%) as a colorless oil.

Analytical data for I.88:

TLC (20% ethyl acetate in hexanes), R_f = 0.58 (UV, $KMnO_4$).

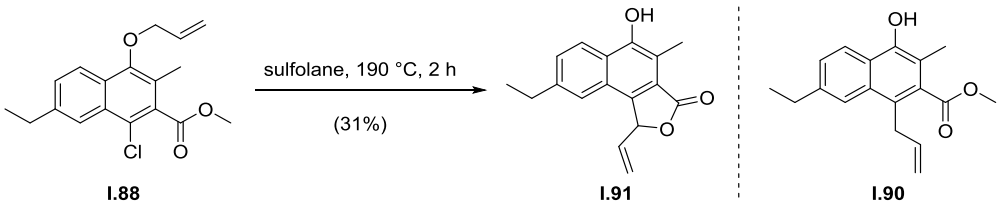
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 8.01 (d, *J* = 6.6 Hz, 1H), 7.45 (dd, *J* = 8.6, 0.9 Hz, 1H), 6.18 (ddt, *J* = 17.1, 11.6, 5.9 Hz, 1H), 5.50 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 4.45 (d, *J* = 6.6 Hz, 2H), 4.01 (s, 3H), 2.85 (q, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.2, 152.1, 143.6, 133.6, 133.3, 130.4, 129.0, 127.9, 123.4, 123.0 (2C), 122.6, 118.0, 75.2, 52.8, 29.3, 15.6, 13.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 287 (*w*), 1736 (*vs*), 1598 (*w*), 1436 (*m*), 1385 (*m*), 1330 (*m*), 1315 (*m*), 1280 (*m*), 1231 (*s*), 1214 (*m*), 1170 (*m*), 1113 (*m*), 1051 (*s*), 991 (*m*), 972 (*m*), 937 (*m*), 877 (*m*), 833 (*m*), 757 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{19}O_3{}^{35}Cl$ $[M]^+$: 318.1017; found: 318.1020.

8-Ethyl-5-hydroxy-4-methyl-1-vinylnaphtho[1,2-c]furan-3(1H)-one (I.91):



I.88 I.91 I.90

A solution of **I.88** (1.56 g, 4.90 mmol, 1 equiv) in sulfolane (10 mL) was heated to 190 °C. After 2 h, water (100 mL) and diethyl ether (100 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed successively with water (5 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **I.91** (407.7 mg, 31%) as a yellow solid.

Note: When the reaction time was shortened to only 5 min, the p-allylated naphthol ***I.90*** *was isolated as main product in 25% yield.*

Analytical data for I.91:

TLC (20% ethyl acetate in hexanes), R_f = 0.23 (UV, CAM, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 1.0 Hz, 1H), 7.53 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.04 (d, *J* = 7.8 Hz, 1H), 5.92 (ddd, *J* = 17.0, 9.9, 7.7 Hz, 1H), 5.75 (d, *J* = 16.8 Hz, 1H), 5.52 (d, *J* = 10.3 Hz, 1H), 5.50 (s, 1H), 2.83 (q, *J* = 7.5 Hz, 2H), 2.70 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.4, 150.8, 143.4, 140.0, 134.7, 129.8, 126.6, 125.8, 123.1, 122.0, 121.7, 121.2, 112.4, 80.7, 29.1, 15.4, 9.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3418 (*w*), 2966 (*w*), 1733 (*vs*), 1582 (*w*), 1469 (*w*), 1395 (*w*), 1371 (*w*), 1299 (*w*), 1262 (*w*), 1198 (*w*), 1013 (*m*), 977 (*m*), 939 (*w*), 834 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{16}O_3$ $[M]^+$: 268.1094; found: 268.1074.

Analytical data for I.90:

TLC (20% ethyl acetate in hexanes), R_f = 0.28 (UV, $KMnO_4$).

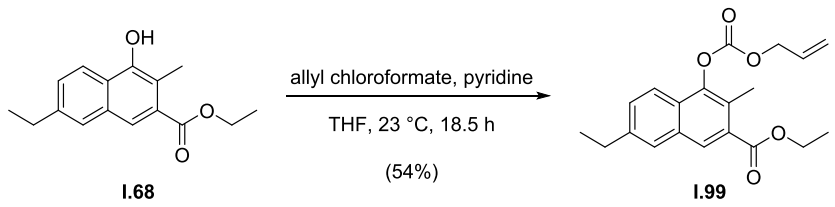
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.04 – 5.96 (m, 1H), 5.13 (s, 1H), 5.05 – 5.00 (m, 2H), 3.95 (s, 3H), 3.69 (d, *J* = 6.7 Hz, 2H), 2.81 (q, *J* = 7.6 Hz, 3H), 2.30 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 170.8, 147.9, 142.2, 136.9, 133.5, 131.6, 127.3, 124.6, 123.4, 122.9, 121.6, 115.8, 111.7, 52.2, 34.4, 29.4, 15.6, 13.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3472 (*w*), 2965 (*w*), 2932 (*w*), 1728 (*vs*), 1664 (*w*), 1601 (*m*), 1505 (*w*), 1437 (*m*), 1389 (*m*), 1366 (*m*), 1282 (*m*), 1232 (*s*), 1194 (*m*), 1175 (*m*), 1115 (*w*), 1061 (*m*), 991 (*w*), 914 (*w*), 832 (*w*), 754 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1407; found: 284.1410.

Ethyl 4-(((allyloxy)carbonyl)oxy)-7-ethyl-3-methyl-2-naphthoate (I.99):



I.68 I.99

To a solution of **I.68** (250 mg, 0.968 mmol, 1 equiv) in tetrahydrofuran (4.8 mL) was added pyridine (0.110 mL, 1.35 mmol, 1.40 equiv). After cooling to 0 °C, allyl chloroformate (0.123 mL, 1.16 mmol, 1.20 equiv) was added. The reaction mixture was stirred for 5 min at 0 °C and then 18.5 h at 23 °C. Water (5 mL) and ethyl acetate (5 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with aqueous hydrogen chloride solution (2 M, 2 × 20 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes) to afford **I.99** (178 mg, 54%) as a colorless oil.

Analytical data for I.99:

TLC (20% ethyl acetate in hexanes), R_f = 0.50 (UV, $KMnO_4$).

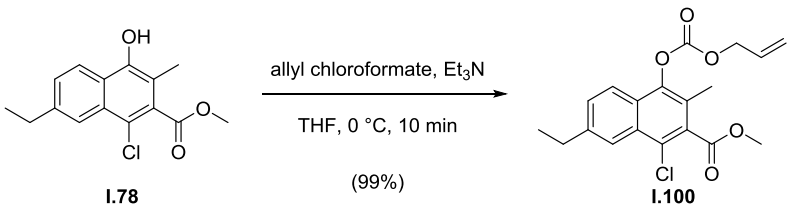
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.69 (s, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 6.04 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.47 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.36 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.80 (dt, *J* = 5.8, 1.3 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.81 (q, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.4, 153.2, 145.3, 142.6, 132.0, 131.2, 130.4, 129.5, 129.3, 127.1, 126.7, 126.0, 120.8, 119.7, 69.5, 61.2, 28.9, 15.4, 14.5, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*w*), 1762 (*s*), 1718 (*s*), 1604 (*w*), 1456 (*w*), 1364 (*w*), 1287 (*w*), 1287 (*m*), 1231 (*vs*), 1205 (*s*), 1169 (*m*), 1037 (*m*), 973 (*m*), 915 (*m*), 829 (*m*), 780 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{22}O_5$ $[M]^+$: 342.1462; found: 342.1470.

Methyl 4-(((allyloxy)carbonyl)oxy)-1-chloro-7-ethyl-3-methyl-2-naphthoate (I.100):



I.78 I.100

To a solution of **I.78** (4.00 g, 14.4 mmol, 1 equiv) in tetrahydrofuran (72 mL) was added triethylamine (2.79 mL, 20.1 mmol, 1.40 equiv), the mixture was cooled to 0 °C and allyl chloroformate (1.83 mL, 17.2 mmol, 1.20 equiv) was added. After 10 min, saturated aqueous ammonium chloride solution (100 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous hydrogen chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The product **I.100** (5.15 g, 99%) was obtained as an orange oil and used without further purification.

Analytical data for I.100:

TLC (20% ethyl acetate in hexanes), R_f = 0.43 (UV, $KMnO_4$).

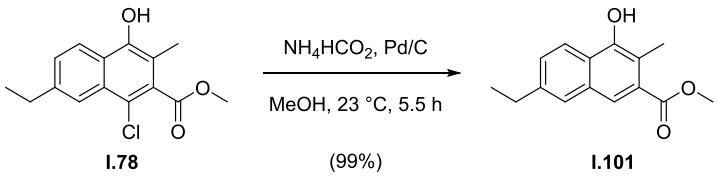
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 1.8 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.49 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.24 – 5.78 (m, 1H), 5.46 (dq, *J* = 16.9, 1.5 Hz, 1H), 5.37 (dq, *J* = 10.6, 1.3 Hz, 1H), 4.88 – 4.59 (m, 2H), 4.01 (s, 3H), 2.85 (q, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.33 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.6, 152.9, 144.1, 143.8, 132.8, 131.1, 130.2, 129.9, 126.5, 126.2, 123.3, 123.1, 121.3, 120.0, 69.8, 52.9, 29.3, 15.6, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2361 (*m*), 1764 (*m*), 1736 (*m*), 1437 (*w*), 1232 (*vs*), 940 (*w*), 668 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{20}O_5{}^{35}Cl$ $[M]^+$: 362.0916; found: 362.0917.

Methyl 7-ethyl-4-hydroxy-3-methyl-2-naphthoate (I.101):



I.78 (99%) **I.101**

To a solution of **I.78** (1.00 g, 3.59 mmol, 1 equiv) in methanol (13.8 mL) were added ammonium formate (1.36 g, 21.5 mmol, 6.00 equiv) and Pd/C (10% Pd on activated charcoal, 382 mg, 0.359 mmol, 0.100 equiv). After 5.5 h, the reaction mixture was filtered through a short pad of Celite® and washed successively with diethyl ether (50 mL). Water (50 mL) and aqueous hydrochloric acid solution (2 M, 50 mL) were added and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated aqueous hydrogen chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The product **I.101** (865 mg, 99%) was obtained as a beige solid and used without further purification.

Analytical data for I.101:

TLC (20% ethyl acetate in hexanes), R_f = 0.33 (UV, $KMnO_4$).

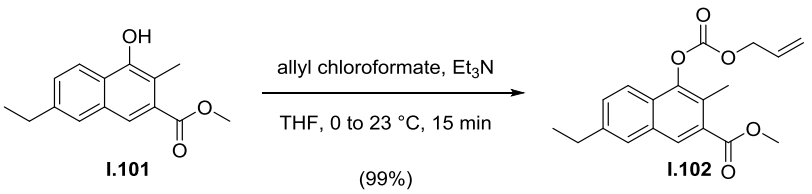
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.6 Hz, 1H), 7.99 (s, 1H), 7.60 (s, 1H), 7.42 (dd, *J* = 8.6, 1.7 Hz, 1H), 5.41 (s, 1H), 3.95 (s, 3H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.58 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.8, 149.5, 142.3, 132.0, 129.1, 128.9, 126.4, 124.4, 123.7, 121.3, 115.1, 52.3, 29.0, 15.5, 12.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3501 (*m*), 2952 (*w*), 1697 (*vs*), 1597 (*m*), 1573 (*m*), 1436 (*m*), 1375 (*s*), 1326 (*m*), 1280 (*s*), 1220 (*vs*), 1174 (*s*), 1114 (*m*), 1065 (*m*), 1050 (*vs*), 999 (*s*), 938 (*s*), 899 (*s*), 838 (*s*), 775 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1094; found: 244.1093.

Methyl 4-(((allyloxy)carbonyl)oxy)-7-ethyl-3-methyl-2-naphthoate (I.102):



To a solution of **I.101** (268 mg, 1.10 mmol, 1 equiv) in tetrahydrofuran (5.5 mL) was added triethylamine (0.213 mL, 1.54 mmol, 1.20 equiv), the mixture was cooled to 0 °C and allyl chloroformate (0.140 mL, 1.32 mmol, 1.40 equiv) was added. After 5 min, the ice bath was removed and after further 10 min, saturated aqueous ammonium chloride solution (40 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. **I.102** (358 mg, 99%) was obtained as a yellow oil and used without further purification.

Analytical data for I.102:

TLC (20% ethyl acetate in hexanes), R_f = 0.49 (UV, CAM, $KMnO_4$).

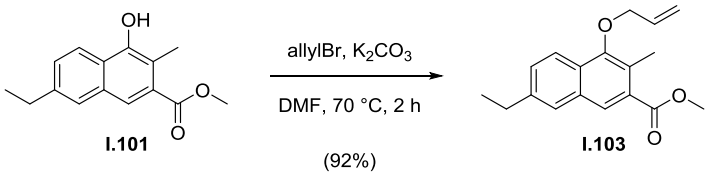
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.47 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.04 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.47 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.36 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.80 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.94 (s, 3H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.58 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.7, 153.1, 145.3, 142.6, 131.9, 131.2, 130.4, 129.7, 128.8, 127.1, 126.7, 126.0, 120.7, 119.7, 69.5, 52.2, 28.9, 15.3, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 1760 (*s*), 1719 (*s*), 1605 (*w*), 1435 (*m*), 1361 (*w*), 1288 (*m*), 1225 (*vs*), 1203 (*vs*), 1165 (*s*), 1117 (*m*), 1034 (*m*), 987 (*m*), 939 (*m*), 913 (*m*), 827 (*m*), 778 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{20}O_5$ $[M]^+$: 238.1305; found: 328.1305.

Methyl 4-(allyloxy)-7-ethyl-3-methyl-2-naphthoate (I.103):



To a solution of **I.101** (500 mg, 2.05 mmol, 1 equiv) in dimethylformamide (7 mL) were subsequently added potassium carbonate (424 mg, 3.07 mmol, 1.50 equiv) and allyl bromide (0.195 mL, 2.25 mmol, 1.10 equiv) and the suspension was heated to 70 °C. After 2 h, saturated aqueous ammonium chloride solution (50 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 70 mL). The combined organic layers were washed with aqueous hydrochloric acid solution (2 M, 50 mL) and saturated aqueous hydrogen chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to yield **I.103** (538 mg, 92%) as a colorless oil.

Analytical data for I.103:

TLC (20% ethyl acetate in hexanes), R_f = 0.58 (UV, $KMnO_4$).

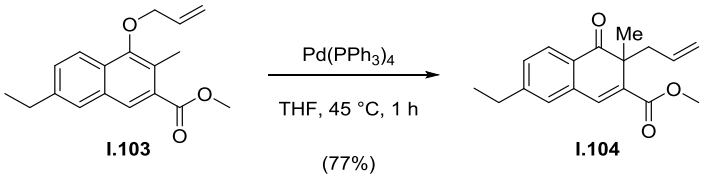
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.44 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.21 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.52 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.33 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.47 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.95 (s, 3H), 2.81 (q, *J* = 7.6 Hz, 2H), 2.63 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.5, 153.4, 142.2, 133.9, 132.4, 129.6, 129.5, 128.5, 127.3, 126.7, 125.8, 122.2, 117.7, 74.8, 52.2, 29.0, 15.5, 13.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 1722 (*vs*), 1598 (*w*), 1452 (*w*), 1435 (*m*), 1331 (*m*), 1284 (*s*), 1237 (*m*), 1205 (*m*), 1111 (*m*), 1048 (*s*), 1014 (*m*), 910 (*m*), 832 (*m*), 780 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1407; found: 284.1403.

Methyl 3-allyl-7-ethyl-3-methyl-4-oxo-3,4-dihydronaphthalene-2-carboxylate (I.104):



Tetrakis(triphenylphosphine)palladium(0) (223 mg, 0.189 mmol, 0.100 mmol) was added to a Schlenk flask and the flask was purged with argon. **I.103** (538 mg, 1.89 mmol, 1 equiv) was added and the flask was again purged with argon. The reactants were dissolved in degassed tetrahydrofuran (63 mL) and stirred at 45 °C for 1 h. The reaction mixture was filtered through a plug of silica gel and rinsed thoroughly with diethyl ether (100 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to obtain **I.104** (416 mg, 77%) as a colorless oil.

Analytical data for I.104:

TLC (20% ethyl acetate in hexanes), R_f = 0.51 (UV, CAM, $KMnO_4$).

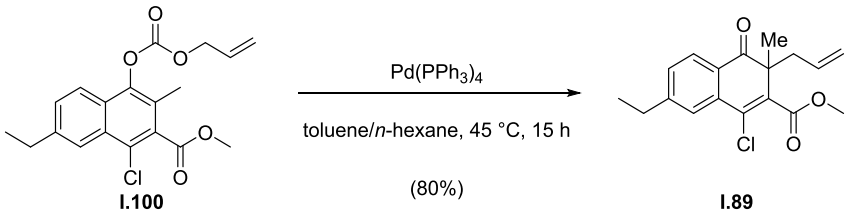
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 7.9 Hz, 1H), 7.72 (s, 1H), 7.34 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.22 (d, *J* = 1.2 Hz, 1H), 5.43 – 5.30 (m, 1H), 4.94 – 4.83 (m, 1H), 4.77 (ddt, *J* = 10.2, 2.1, 1.0 Hz, 1H), 3.84 (s, 3H), 3.10 – 2.85 (m, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.50 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.8, 166.2, 151.8, 137.3, 135.8, 134.9, 134.1, 130.4, 128.8, 127.8, 127.6, 117.4, 52.0, 51.5, 43.0, 29.2, 25.1, 15.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2969 (*w*), 1714 (*vs*), 1673 (*s*), 1640 (*w*), 1599 (*m*), 1453 (*m*), 1374(*w*), 1281 (*m*), 1245 (*s*), 1219 (*vs*), 1044 (*w*), 989 (*w*), 920 (*w*), 848 (*w*), 778 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1407; found: 284.1406.

Methyl 3-allyl-1-chloro-7-ethyl-3-methyl-4-oxo-3,4-dihydronaphthalene-2-carboxylate (I.89):



Tetrakis(triphenylphosphine)palladium(0) (669 mg, 0.579 mmol, 7.00mol%) was added to a Schlenk flask and the flask was purged with argon. **I.100** (3.00 g, 8.27 mmol, 1 equiv) was added and the flask was again purged with argon. The reactants were dissolved in degassed toluene (219 mL) and degassed *n*-hexanes (22 mL) and stirred at 45 °C for 15 h. The reaction mixture was filtered through a plug of silica gel and rinsed thoroughly with diethyl ether (200 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to obtain **I.89** (2.1 g, 80%) as a light yellow oil.

Analytical data for I.89:

TLC (20% ethyl acetate in hexanes), R_f = 0.44 (UV, $KMnO_4$)

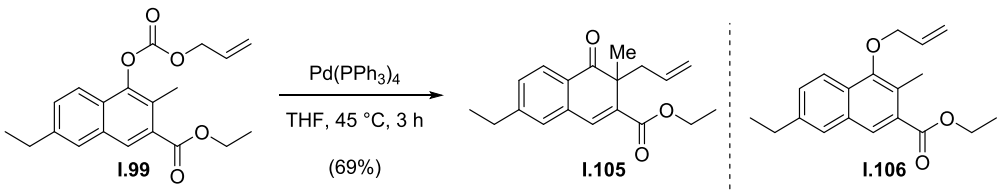
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.7 Hz, 1H), 5.74 – 5.32 (m, 1H), 4.99 (dt, *J* = 17.0, 1.6 Hz, 1H), 4.93 – 4.77 (m, 1H), 3.91 (s, 3H), 2.76 (p, *J* = 7.6 Hz, 3H), 2.52 (dd, *J* = 13.7, 6.5 Hz, 1H), 1.41 (s, 3H), 1.30 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.4, 166.4, 151.9, 137.9, 134.4, 132.2, 129.7, 127.7, 127.6, 127.5, 125.4, 118.8, 52.5, 52.3, 44.2, 29.3, 23.7, 15.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (*w*), 1729 (*vs*), 1679 (*m*), 1598 (*m*), 1453 (*w*), 1434 (*m*), 1284 (*m*), 1248 (*m*), 1231 (*m*), 1195 (*m*), 1044 (*w*), 994 (*w*), 924 (*w*), 848 (*w*) 701 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{19}O_3{}^{35}Cl$ $[M]^+$: 318.1017; found: 318.1016.

Ethyl 3-allyl-7-ethyl-3-methyl-4-oxo-3,4-dihydronaphthalene-2-carboxylate (I.105):



A solution of **I.99** (91.0 mg, 0.266 mmol, 1 equiv) in degassed tetrahydrofuran (5.3 mL) was added to a solution of tetrakis(triphenylphosphane)palladium(0) (31.3 mg, 0.0271 mmol; 0.102 equiv) in degassed tetrahydrofuran (3.3 mL). The reaction was heated to 45 °C for 3 h, cooled to 23 °C and diluted with diethyl ether (5 mL). The reaction mixture was filtered through a short plug of silica and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to afford **I.105** (54 mg, 69%) as a yellow oil.

*Note: During the screening for the optimal reaction conditions, the o-product **I.106** was isolated and analyzed.*

Analytical data for I.105:

TLC (20% ethyl acetate in hexanes), R_f = 0.53 (UV, $KMnO_4$).

^{1}H NMR (800 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 7.9 Hz, 1H), 7.72 (s, 1H), 7.33 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 5.35 (dddd, *J* = 16.8, 10.1, 8.2, 6.6 Hz, 1H), 4.89 (ddd, *J* = 16.9, 3.4, 1.3 Hz, 1H), 4.77 (ddt, *J* = 10.3, 1.9, 0.7 Hz, 1H), 4.30 (qd, *J* = 7.2, 4.0 Hz, 2H), 3.06 (dd, *J* = 13.7, 8.1 Hz, 1H), 2.90 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.74 (q, *J* = 7.7 Hz, 2H), 1.51 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ: 201.9, 165.8, 151.8, 137.6, 135.9, 134.6, 134.1, 130.3, 128.8, 127.8, 127.6, 117.4, 60.9, 51.6, 43.0, 29.2, 25.1, 15.2, 14.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (*w*), 2935 (*w*), 2360 (*w*), 1712 (*vs*), 1674 (*s*), 1600 (*m*), 1456 (*w*), 1375 (*w*), 1281 (*m*), 1245 (*m*), 1218 (*vs*), 1045 (*w*), 990 (*w*), 920 (*w*), 848 (*w*), 777 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1563; found: 298.1567.

Analytical data for I.106:

TLC (20% ethyl acetate in hexanes), R_f = 0.62 (UV).

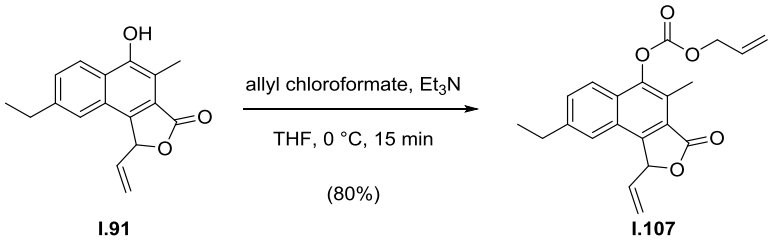
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.44 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.22 (ddt, *J* = 17.2, 10.8, 5.5 Hz, 1H), 5.52 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.33 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.47 (dt, *J* = 5.6, 1.5 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.81 (q, *J* = 7.6 Hz, 2H), 2.63 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.1, 153.3, 142.2, 133.9, 132.4, 130.0, 129.5, 128.4, 127.1, 126.7, 125.7, 122.2, 117.7, 74.8, 61.1, 29.0, 15.5, 14.5, 13.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (*w*), 2932 (*w*), 1715 (*vs*), 1599 (*w*), 1568 (*w*), 1452 (*m*), 1385 (*m*), 1374 (*m*), 1315 (*m*), 1281 (*vs*), 1236 (*s*), 1201 (*vs*), 1170 (*m*), 1110 (*m*), 1045 (*vs*), 1009 (*s*), 992 (*s*), 910 (*s*), 832 (*s*), 779 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1563; found: 298.1562.

Allyl (8-ethyl-4-methyl-3-oxo-1-vinyl-1,3-dihydronaphtho[1,2-c]furan-5-yl) carbonate (I.107):



I.91 **I.107**

To a solution of **I.91** (500 mg, 1.86 mmol, 1 equiv) in tetrahydrofuran (9.3 mL) was added triethylamine (0.363 mL, 2.61 mmol, 1.40 equiv). After 10 min, the reaction mixture was cooled to 0 °C and allyl chloroformate (0.238 mL, 2.24 mmol, 1.20 equiv) was added. After 15 min, water (100 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (70 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **I.107** (528 mg, 80%) as a light yellow solid.

Analytical data for I.107:

TLC (20% ethyl acetate in hexanes), R_f = 0.35 (UV, CAM, $KMnO_4$).

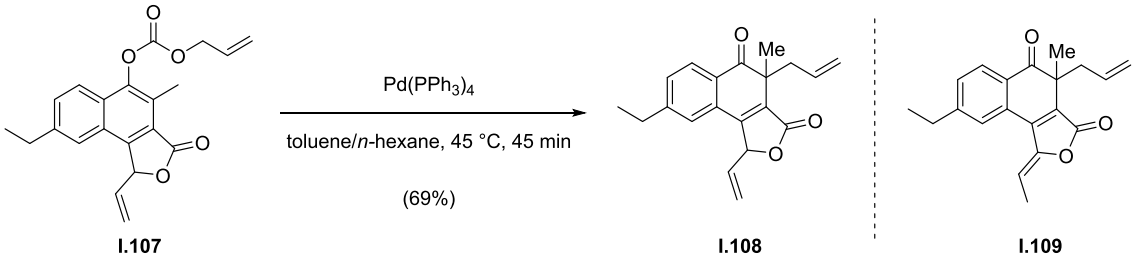
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 8.7 Hz, 1H), 7.71 (d, *J* = 0.8 Hz, 1H), 7.57 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.10 (d, *J* = 7.7 Hz, 1H), 6.10 – 5.88 (m, 2H), 5.80 (d, *J* = 16.7 Hz, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 5.48 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.39 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.81 (dt, *J* = 5.8, 1.3 Hz, 2H), 2.83 (q, *J* = 7.6 Hz, 2H), 2.66 (s, 3H), 1.31 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.4, 153.0, 146.1, 145.7, 143.8, 134.0, 131.3, 131.0, 128.5, 126.7, 124.4, 122.3, 122.3, 122.1, 121.8, 120.1, 80.7, 69.8, 29.1, 15.4, 10.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2921 (*w*), 1746 (*vs*), 1610 (*w*), 1411 (*w*), 1356 (*w*), 1304 (*w*), 1232 (*s*), 1196 (*m*), 1147 (*m*), 1027 (*m*), 1013 (*m*), 972 (*m*), 938 (*m*), 924 (*m*), 886 (*m*), 840 (*m*), 778 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{20}O_5$ $[M]^+$: 352.1305; found: 352.1309.

4-Allyl-8-ethyl-4-methyl-1-vinyl-1,4-dihydronaphtho[1,2-c]furan-3,5-dione (I.108):



I.107 **I.108** **I.109**

Tetrakis(triphenylphosphine)palladium(0) (32.8 mg, 0.0284 mmol, 0.100 equiv) was added to a Schlenk flask and the flask was purged with argon. **I.107** (100 mg, 0.284 mmol, 1 equiv) was added and the flask was again purged with argon. The reactants were dissolved in degassed toluene (7.5 mL) and degassed *n*-hexanes (0.75 mL) and stirred at 45 °C for 45 min. The reaction mixture was filtered through a plug of silica gel and rinsed thoroughly with diethyl ether (100 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **I.108** (60 mg, 69%, mixture of diastereomers) as a yellow oil.

Note: A small sample of the diastereomeric mixture was used to separate the diastereomers by flash column chromatography on silica gel (5% ethyl acetate in hexanes).

Analytical data for the major isomer I.108:

TLC (20% ethyl acetate in hexanes), R_f = 0.29 (UV, $KMnO_4$).

^{1}H NMR (800 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.28 – 7.26 (m, 1H), 5.89 (ddd, *J* = 17.0, 10.0, 7.9 Hz, 1H), 5.77 (d, *J* = 8.4 Hz, 1H), 5.76 (d, *J* = 17.0 Hz, 1H), 5.57 (d, *J* = 10.0 Hz, 1H), 5.33 (dddd, *J* = 16.8, 10.1, 8.2, 6.6 Hz, 1H), 4.97 (dq, *J* = 16.9, 1.3 Hz, 1H), 4.80 (dd, *J* = 10.1, 1.9 Hz, 1H), 2.96 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.81 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.74 (qd, *J* = 7.5, 2.9 Hz, 2H), 1.53 (s, 3H), 1.28 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ: 200.8, 170.0, 153.0, 151.7, 133.5, 132.8, 132.4, 131.4, 130.7, 128.9, 128.3, 124.4, 122.5, 118.7, 80.5, 48.6, 42.6, 29.2, 23.1, 15.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2920 (*m*), 2363 (*w*), 1756 (*vs*), 1679 (*m*), 1600 (*m*), 1456 (*w*), 1378 (*w*), 1239 (*m*), 1015 (*m*), 853 (*w*), 797 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.1407; found: 308.1410.

Analytical data for I.109:

TLC (20% ethyl acetate in hexanes), R_f = 0.43 (UV, $KMnO_4$).

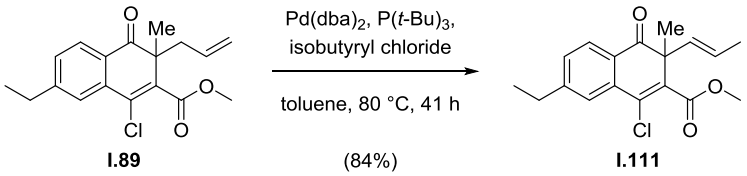
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.06 (q, *J* = 7.2 Hz, 1H), 5.40 – 5.31 (m, 1H), 4.96 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.81 (dd, *J* = 10.3, 2.0 Hz, 1H), 2.96 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.84 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.79 (q, *J* = 7.6 Hz, 2H), 2.11 (d, *J* = 7.2 Hz, 3H), 1.51 (s, 3H), 1.33 (d, *J* = 7.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 200.3, 166.6, 151.6, 146.8, 141.4, 132.9, 132.4, 130.9, 130.5, 129.4, 128.8, 124.8, 118.7, 111.6, 48.4, 42.4, 29.4, 23.2, 15.3, 12.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (*w*), 1764 (*vs*), 1680 (*m*), 1594 (*m*), 1452 (*w*), 1389 (*w*), 1315 (*w*), 1246 (*m*), 1012 (*m*), 921 (*w*), 851 (*w*), 772 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.1407; found: 308.1401.

Methyl (*E*)-1-chloro-7-ethyl-3-methyl-4-oxo-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.111):



I.89 **I.111**

To bis(dibenzylidenacetone)palladium(0) (113 mg, 0.0196 mmol, 10.0 mol%) was added subsequently a solution of **I.89** (625 mg, 1.96 mmol, 1 equiv) in degassed toluene (5.3 mL), tri-*t*-butylphosphine (1 M in toluene, 0.196 mL, 0.196 mmol, 10.0 mol%) and isobutyryl chloride (0.078M in degassed toluene, 2.51 mL, 0.196 mmol, 10.0 mol%). The reaction mixture was heated to 80 °C for 41 h and then diluted with ethyl acetate (50 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to afford **I.111** (523 mg, 84%) as a yellow oil. **Analytical data for I.111:**

*Note: The product **I.111** could not be separated from traces of remaining starting material **I.89**, since both were co-polar during column chromatography.*

TLC (20% ethyl acetate in hexanes), R_f = 0.56 (UV, $KMnO_4$).

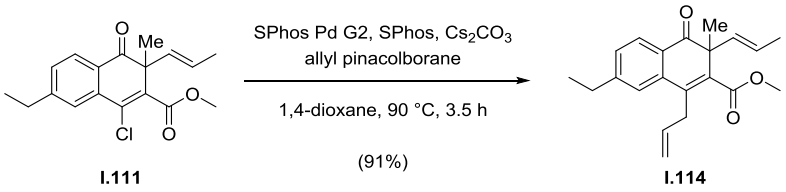
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.33 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.67 (dq, *J* = 15.6, 6.5 Hz, 1H), 5.43 (dq, *J* = 15.4, 1.6 Hz, 1H), 3.85 (s, 3H), 2.76 (q, *J* = 7.6 Hz, 2H), 1.65 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.52 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 197.0, 166.4, 151.9, 137.8, 134.3, 129.8, 129.7, 128.4, 128.2, 127.3, 127.3, 125.6, 54.2, 52.4, 29.4, 21.5, 18.2, 15.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*w*), 1729 (*vs*), 1683 (*s*), 1598 (*s*), 1447 (*m*), 1433 (*m*), 1373 (*w*), 1270 (*vs*), 1230 (*s*), 1198 (*s*), 1121 (*m*), 1061 (*m*), 1043 (*s*), 983 (*m*), 958 (*s*), 846 (*m*), 806 (*m*), 698 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{19}O_3{}^{35}Cl$ $[M]^+$: 318.1017; found: 318.1014.

Methyl (E)-1-allyl-7-ethyl-3-methyl-4-oxo-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.114):



A mixture of **I.111** (88 mg, 0.276 mmol, 1 equiv), cesium carbonate (360 mg, 1.10 mmol, 4.00 equiv), SPhos-Pd-G2 (19.9 mg, 0.0276 mmol, 0.100 equiv) and SPhos (34.0 mg, 0.0828 mmol, 0.300 equiv) was dissolved in degassed dioxane (3.9 mL), then allylboronic acid pinacol ester (0.207 mL, 1.10 mmol, 4.00 equiv) was added and the reaction mixture was heated to 90 °C. After 3.5 h, water (40 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to yield **I.114** (81 mg, 91%) as a light yellow oil.

Analytical data for I.114:

TLC (toluene), R_f = 0.43 (UV, $KMnO_4$).

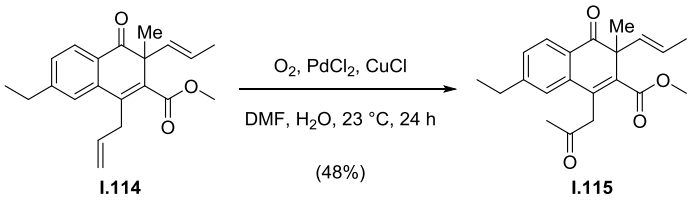
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.31 (m, 1H), 7.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.2, 6.0 Hz, 1H), 5.63 (dq, *J* = 15.7, 6.5 Hz, 1H), 5.45 (dq, *J* = 15.4, 1.6 Hz, 1H), 5.16 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.11 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.79 (s, 3H), 3.34 (qdt, *J* = 16.0, 5.9, 1.7 Hz, 2H), 2.72 (q, *J* = 7.6 Hz, 2H), 1.65 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.49 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.1, 168.8, 151.2, 138.8, 136.6, 135.3, 130.9, 130.8, 128.6, 128.1, 127.6, 127.5, 125.2, 117.1, 52.3, 51.8, 34.6, 29.5, 21.5, 18.3, 15.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*w*), 2875 (*w*), 1724 (*vs*), 1682 (*s*), 1601 (*m*), 1449 (*w*), 1433 (*w*), 1373 (*w*), 1285 (*m*), 1237 (*s*), 1195 (*m*), 1061 (*w*), 1021 (*w*), 983 (*w*), 963 (*w*), 916 (*w*), 846 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{24}O_3$ $[M]^+$: 324.1720; found: 324.1724.

Methyl (E)-7-ethyl-3-methyl-4-oxo-1-(2-oxopropyl)-3-(prop-1-en-1-yl)-3,4-dihydron aphthalene-2-carboxylate (I.115):



I.114 I.115

A suspension of **I.114** (60.0 mg, 0.185 mmol, 1 equiv), palladium(II) chloride (6.56 mg, 0.0370 mmol, 0.200 equiv) and copper(I) chloride (20.1 mg, 0.203 mmol, 1.10 equiv) in water (0.6 mL) and dimethylformamide (10.5 mL) was sparged with oxygen gas for 1 min. An oxygen balloon stayed attached and after 24 h, the reaction mixture was diluted with aqueous hydrochloric acid solution (2 M, 50 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **I.115** (30 mg, 48%) as a yellow oil.

Analytical data for I.115:

TLC (20% ethyl acetate in hexanes), R_f =0.20 (UV, $KMnO_4$).

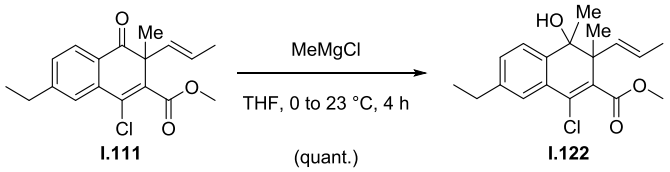
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.13 (d, *J* = 1.5 Hz, 1H), 5.66 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.47 (dq, *J* = 15.5, 1.6 Hz, 1H), 3.80 (s, 3H), 3.76 – 3.61 (m, 2H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.65 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.53 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 205.8, 198.6, 168.5, 151.7, 140.5, 136.5, 130.5, 129.1, 128.4, 128.4, 127.9, 127.2, 124.6, 52.5, 52.1, 46.0, 29.4, 29.1, 21.6, 18.3, 15.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (*w*), 1717 (*vs*), 1679 (*s*), 1600 (*s*), 1432 (*m*), 1358 (*w*), 1286 (*s*), 1237 (*vs*), 1196 (*m*), 1159 (*m*), 1064 (*w*), 1033 (*m*), 981 (*m*), 964 (*m*), 913 (*w*), 847 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{24}O_4$ $[M]^+$: 340.1669; found: 340.1670.

Methyl (E)-1-chloro-7-ethyl-4-hydroxy-3,4-dimethyl-3-(prop-1-en-1-yl)-3,4-dihydro naphthalene-2-carboxylate (I.122):



To a solution of **I.111** (250 mg, 0.784 mmol, 1 equiv) in tetrahydrofuran (9 mL) was added methylmagnesium chloride solution (3 M in tetrahydrofuran, 1.57 mL, 4.71 mmol, 6 equiv) at 0 °C. The reaction mixture was allowed to warm to 23 °C and after 4 h, saturated aqueous sodium bicarbonate solution (30 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to yield **I.122** (255 mg, quant., 1:1.3 mixture of diastereomers) as a colorless oil.

Analytical data for I.122:

Note: The singals, which could be assigned to the major diastereomer, are marked with ‡. Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk. Due to severe signal broadening in the ^{13}C NMR spectra some signals are missing.

TLC (20% ethyl acetate in hexanes), R_f = 0.39 (UV, CAM, $KMnO_4$).

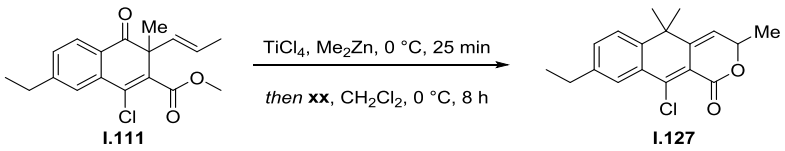
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 – 7.41 (m, 4H), 7.25 – 7.16 (m, 2H), 5.86 – 5.61 (m, 3H), 5.42 (d, *J* = 15.7 Hz, 1H), 3.82 (s, 3H)‡, 3.80 (s, 3H), 2.67 (q, *J* = 7.6 Hz, 4H), 1.98 (s, 1H)‡, 1.86 (s, 1H), 1.78 – 1.69 (m, 3H), 1.65 (dd, *J* = 6.5, 1.6 Hz, 3H)‡, 1.46 (s, 3H), 1.40 (s, 3H)‡, 1.32 – 1.21 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.5, 167.3‡, 143.7, 143.5‡, 141.4*, 139.6, 136.9, 136.0, 130.6, 130.0, 129.9, 129.9, 129.7, 129.2, 128.8, 128.6, 128.3, 125.1, 125.1, 124.1, 124.0‡, 75.8, 75.2‡, 52.1‡, 52.1, 50.2, 49.4, 28.7 (2C), 25.6*, 23.8*, 18.6, 18.4, 16.7, 15.6, 15.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3522 (*w*), 2966 (*w*), 1728 (*vs*), 1624 (*w*), 1606 (*w*), 1433 (*m*), 1370 (*m*), 1370 (*vs*), 1196 (*m*), 1169 (*m*), 1145 (*s*), 1090 (*m*), 1041 (*s*), 965 (*m*), 931 (*m*), 838 (*m*), 766 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{23}O_3{}^{35}Cl$ $[M]^+$: 334.1330; found: 334.1339.

10-Chloro-8-ethyl-3,5,5-trimethyl-3,5-dihydro-1H-benzo[g]isochromen-1-one (I.127):



To titanium(IV) chloride (1 M in dichloromethane, 0.941 mL, 0.941 mmol, 6.00 equiv) in a Schlenk tube, which was wrapped in aluminum foil, was added dimethylzinc (15wt% in toluene, 0.784 mL, 0.941 mmol, 6.00 equiv) over 5 min at 0 °C. After 25 min, a solution of **I.111** (50.0 mg, 0.157 mmol, 1 equiv) in dichloromethane (1.6 mL) was added over 5 min. The reaction mixture was stirred for 8 h at 0 °C before saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to yield **I.127** (29 mg, 61%) as a light yellow oil.

Analytical data for I.127:

TLC (20% ethyl acetate in hexanes), R_f = 0.23 (UV, CAM, $KMnO_4$).

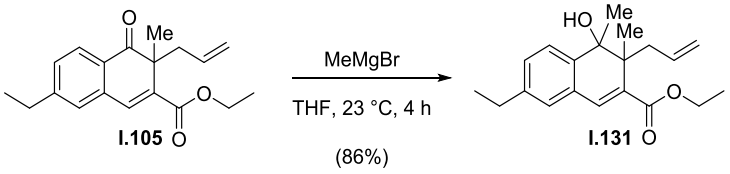
^{1}H NMR (599 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 1.9 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.94 (d, *J* = 2.9 Hz, 1H), 5.03 (qd, *J* = 6.8, 3.2 Hz, 1H), 2.69 (q, *J* = 7.7 Hz, 2H), 1.48 (s, 3H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 3H), 1.26 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 163.6, 143.1, 143.0, 142.6, 136.8, 130.7, 130.2, 127.6, 123.8, 123.3, 117.9, 74.5, 38.3, 28.9, 28.6, 27.2, 22.1, 15.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*m*), 1729 (vs), 1556 (*m*), 1463 (*m*), 1379 (*m*), 1379 (*m*), 1286 (*m*), 1210 (*m*), 1159 (*m*), 895 (*w*), 835 (*w*), 835 (*w*), 786 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{19}O_2{}^{35}Cl$ $[M]^+$: 302.7975; found: 302.1071.

Ethyl 3-allyl-7-ethyl-4-hydroxy-3,4-dimethyl-3,4-dihydronaphthalene-2-carboxylate (I.131):



To a solution of **I.105** (10.0 mg, 0.0335 mmol, 1 equiv) in dry tetrahydrofurane (0.4 mL) was added methylmagnesium bromide solution (1 M in dibutylether, 0.268 mL, 0.268 mmol, 8.00 equiv) at 0 °C. After 5 min, the reaction mixture was warmed to 23 °C and stirred for 4 h. Water (2 mL), saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate (10 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **I.131** (9.06 mg, 86%) as a yellow oil.

Analytical data for I.131:

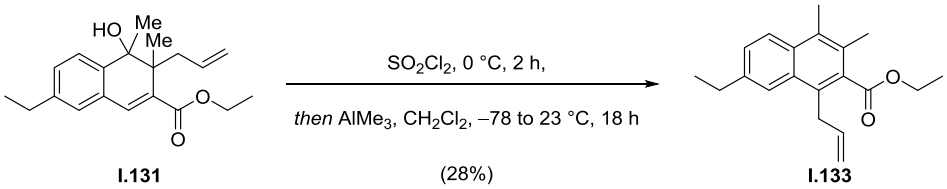
TLC (20% ethyl acetate in hexanes), R_f = 0.48 (UV, $KMnO_4$).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 7.8 Hz, 1H), 7.30 (s, 1H), 7.28 – 7.09 (m, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 5.85 (dtd, *J* = 17.3, 8.8, 6.1 Hz, 1H), 4.96 – 4.80 (m, 2H), 4.24 (qd, *J* = 7.3, 2.8 Hz, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.54 – 2.24 (m, 2H), 1.47 (s, 3H), 1.44 – 1.16 (m, 9H).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3541 (*w*), 2976 (*m*), 1710 (*vs*), 1455 (*w*), 1367 (*m*), 1283 (*m*), 1218 (*vs*), 1184 (*m*), 1043 (*s*), 918 (*m*), 837 (*m*), 776 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{25}O_3$ $[M-H]^-$: 313.1809; found: 313.1794.

Ethyl 1-allyl-7-ethyl-3,4-dimethyl-2-naphthoate (I.133):



I.131 **I.133**

To **I.131** (9.06 mg, 0.0288 mmol, 1 equiv) was added thionly chloride (5.23 μL, 0.720 mmol, 2.50 equiv) at 0 °C. After 2 h, all volatiles were removed under reduced pressure, the remaining mixture was cooled to −78 °C, diluted with dichloromethane (0.11 mL) and trimethylaluminum (2 M in toluene, 28.8 μL, 0.0576 mmol, 2.00 equiv) was added. The reaction mixture was warmed to 23 °C over 18 h, diluted with aqueous hydrochloric acid chloride solution (2 M, 10 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to yield **I.133** (2.4 mg, 28%) as a light yellow oil.

Analytical data for I.133:

TLC (20% ethyl acetate in hexanes), R_f = 0.55 (UV, CAM, $KMnO_4$).

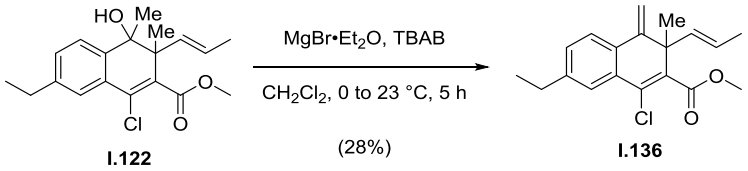
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 8.8 Hz, 1H), 7.80 (s, 1H), 7.39 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.02 (ddt, *J* = 17.4, 9.6, 6.0 Hz, 1H), 5.06 (dd, *J* = 6.3, 1.6 Hz, 1H), 5.03 (t, *J* = 1.5 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 3.75 (d, *J* = 6.6 Hz, 2H), 2.81 (q, *J* = 7.6 Hz, 2H), 2.59 (s, 3H), 2.38 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.2, 141.1, 136.7, 134.0, 131.8, 131.2, 130.4, 129.3, 127.5 (2C), 124.6, 123.1, 116.0, 61.3, 34.8, 29.2, 17.7, 15.7, 14.9, 14.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 2932 (*w*), 1725 (*vs*), 1590 (*w*), 1453 (*w*), 1378 (*w*), 1288 (*w*), 1243 (*m*), 1216 (*m*), 1168 (*m*), 1095 (*w*), 1052 (*m*), 1022 (*w*), 911 (*w*), 820 (*w*) cm^{-1}.

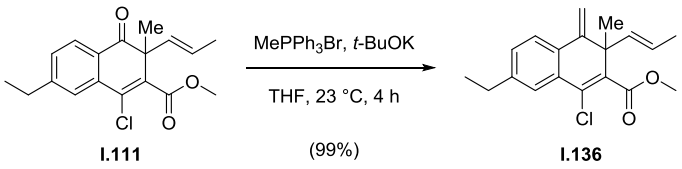
HRMS (EI) calcd for $C_{20}H_{24}O_2$ $[M]^+$: 296.1771; found: 296.1775.

Methyl (E)-1-chloro-7-ethyl-3-methyl-4-methylene-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.136):



A solution of **I.122** (10.0 mg, 0.0299 mmol, 1 equiv) in dichloromethane (1.5 mL) was treated with magnesium bromide diethyl etherate (46.3 mg, 0.179 mmol, 6.00 equiv) and tetrabutylammonium bromide (57.8 mg, 0.179 mmol, 6.00 equiv) at 0 °C. After 10 min, the reaction mixture was warmed to 23 °C. After 5 h, saturated aqueous sodium bicarbonate solution (15 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **I.136** (2.6 mg, 28%) as a yellow oil. For the detailed analytical data see the experiment below.

Methyl (E)-1-chloro-7-ethyl-3-methyl-4-methylene-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.136):



To a solution of methyltriphenylphosphonium bromide (1.03 g, 2.89 mmol, 2.00 equiv) in tetrahydrofuran (14 mL) was added potassium *tert*-butoxide (324 mg, 2.89 mmol, 2.00 equiv). After 1.5 h, the reaction mixture was cooled to 0 °C, a solution of **I.111** (460 mg, 1.44 mmol, 1 equiv) in tetrahydrofuran (9 mL) was added and the reaction mixture was allowed to warm to 23 °C. After 4 h, water (70 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 70 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **I.136** (455 mg, 99%) as a yellow oil.

Analytical data for I.136:

TLC (20% ethyl acetate in hexanes), R_f = 0.56 (UV, CAM, $KMnO_4$).

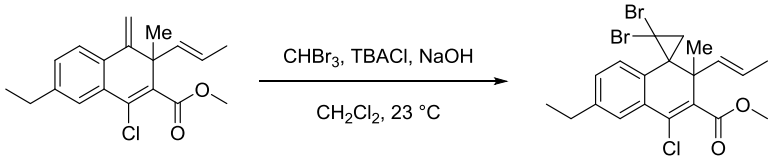
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.67 – 5.56 (m, 2H), 5.44 (s, 1H), 5.18 (s, 1H), 3.80 (s, 3H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.77 – 1.66 (m, 3H), 1.42 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.5, 148.3, 144.8, 136.8, 133.3, 132.2, 129.4, 128.8, 128.3, 125.8, 125.3, 124.7, 112.7, 52.1, 47.3, 28.9, 23.7, 18.2, 15.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (*w*), 1755 (*vs*), 1602 (*w*), 1485 (*w*), 1432 (*m*), 1264 (*s*), 1235 (*s*), 1193 (*m*), 1154 (*m*), 1091 (*w*), 1043 (*m*), 962 (*m*), 898 (*m*), 836 (*m*), 737 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{21}O_2{}^{35}Cl$ $[M]^+$: 316.1225; found: 316.1222.

Methyl (E)-2,2-dibromo-4'-chloro-6'-ethyl-2'-methyl-2'-(prop-1-en-1-yl)-2'H-spiro[cyclopropane-1,1'-naphthalene]-3'-carboxylate (I.137):



I.136 **I.137**

To the substrate **I.136** (40.0 mg, 0.126 mmol, 1 equiv) in dichloromethane (0.5 mL) were added bromoform (13.2 μL, 0.152 mmol, 1.20 equiv) and benzyltriethlammonium chloride (2.88 mg, 0.0126 mmol, 0.100 equiv). An aqueous solution of sodium hydroxide (50wt%, 20.2 μL, 0.253 mmol, 2.00 equiv) was added and the flask was wrapped in aluminum foil. After 2 d, water (10 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated.

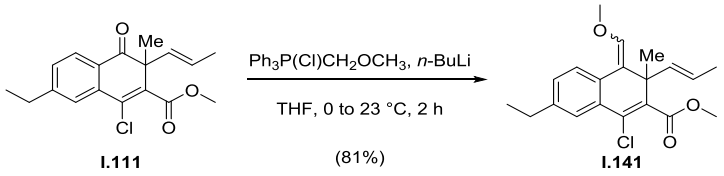
Note: The residue could only be partially purified by flash column chromatography on silica gel for which reason no yield and no NMR and IR data are given.

Analytical data for I.137:

TLC (20% ethyl acetate in hexanes), R_f = 0.54 (UV).

HRMS (EI) calcd for $C_{20}H_{21}O_2{}^{79}Br_2{}^{35}Cl$ $[M]^+$: 485.9591; found: 485.9575.

Methyl 1-chloro-7-ethyl-4-(methoxymethylene)-3-methyl-3-((E)-prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.141):



To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.19 g, 3.48 mmol, 3.70 equiv) in tetrahydrofuran (4.7 mL) was added *n*-butyllithium (2.36 M in hexanes, 1.24 mL, 2.92 mmol, 3.10 equiv) over 5 min at 0 °C. After the addition, the reaction mixture was warmed to 23 °C, stirred at this temperature for 20 min and cooled back to 0 °C. A solution of **I.111** (300 mg, 0.941 mmol, 1 equiv) in tetrahydrofuran (4.7 mL) was added and the reaction mixture was warmed to 23 °C. After 2 h, saturated aqueous ammonium chloride solution (15 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered and concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford **I.141** (265 mg, 81%, inconsequential 1:1 mixture of diastereomers) as a light yellow oil.

Analytical data for I.141:

Note: Singals marked with an asterisk belong to the same diastereomer.

TLC (20% ethyl acetate in hexanes), R_f = 0.47 (UV, CAM).

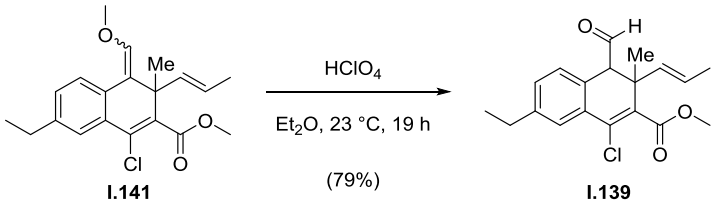
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 8.0 Hz, 1H)*, 7.48 (d, *J* = 1.9 Hz, 1H)*, 7.46 (d, *J* = 1.9 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.9 Hz, 1H)*, 7.07 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.43 (s, 1H), 6.14 (s, 1H)*, 5.73 – 5.63 (m, 1H), 5.62 – 5.57 (m, 1H+1H*), 5.46 (dq, *J* = 15.4, 6.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H)*, 3.70 (s, 3H)*, 3.66 (s, 3H), 2.64 (qd, *J* = 7.6, 5.4 Hz, 2H+2H*), 1.75 – 1.67 (m, 3H)*, 1.64 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.54 (s, 3H), 1.38 (s, 3H)*, 1.24 (td, *J* = 7.6, 3.6 Hz, 3H+3H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 167.5*, 146.8, 145.9*, 142.8, 142.7*, 136.6, 136.6*, 134.6, 133.3*, 131.8, 129.3*, 129.1, 128.9*, 128.7*, 128.7*, 128.5, 128.5*, 128.0, 125.9*, 124.9, 124.7*, 123.4, 123.0, 116.6, 116.4*, 60.8*, 60.7, 52.0, 52.0*, 45.6, 45.3*, 28.9, 28.7*, 24.0*, 23.0, 18.2*, 18.0, 15.6*, 15.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 1748 (*vs*), 1641 (*s*), 1432 (*m*), 1260 (*s*), 1239 (*s*), 1145 (*m*), 1103 (*m*), 1043 (*m*), 977 (*m*), 833 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{23}O_3{}^{35}Cl$ $[M]^+$: 346.1330; found: 346.1330.

Methyl (E)-1-chloro-7-ethyl-4-formyl-3-methyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.139):



To **I.141** (265 mg, 0.764 mmol, 1 equiv) in diethyl ether (13 mL) was added perchloric acid (70% in water, 0.395 mL, 4.56 mmol, 6.00 equiv) and the reaction mixture was vigorously stirred for 19 h. After diluting with diethyl ether (15 mL) and water (15 mL), sodium bicarbonate (400 mg) was added carefully. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered and concentrated. The residue was purified by flash column chromatography on Davisil© (2% ethyl acetate in hexanes) to yield **I.139** (202 mg, 79%, inconsequential mixture of diastereomers) as a colorless oil.

Analytical data for I.139:

Note: The singals, which could be assigned to the major diastereomer, are marked with an asterisk.

TLC (20% ethyl acetate in hexanes), R_f = 0.47 (UV, CAM, $KMnO_4$).

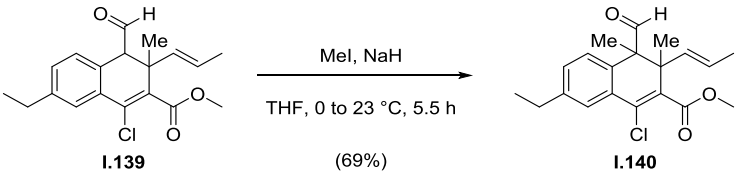
^{1}H NMR (599 MHz, C_6D_6) δ: 9.62 (d, *J* = 4.5 Hz, 1H), 9.54 (d, *J* = 4.5 Hz, 1H)*, 7.63 (d, *J* = 11.9 Hz, 1H+1H*), 6.88 – 6.63 (m, 2H+2H*), 5.77 – 5.59 (m, 1H), 5.51 (dqd, *J* = 15.3, 6.5, 2.4 Hz, 1H+1H*), 5.33 (dd, *J* = 15.6, 2.1 Hz, 1H*), 3.44 (app d, *J* = 4.06 Hz, 3H+3H*), 3.23 (d, *J* = 4.7 Hz, 1H)*, 3.18 (d, *J* = 4.9 Hz, 1H), 2.31 (dq, *J* = 19.5, 7.5 Hz, 2H+2H*), 1.41 (dd, *J* = 6.7, 1.6 Hz, 3H), 1.29 – 1.25 (m, 9H*), 0.99 (t, *J* = 7.7 Hz, 3H), 0.96 (t, *J* = 7.7 Hz, 3H)*.

^{13}C NMR (151 MHz, C_6D_6) δ: 198.0, 197.6*, 166.7*, 145.2, 145.1*, 136.5, 135.1*, 133.3, 131.4, 131.1, 130.6, 130.1, 129.8, 129.3, 129.2, 128.6, 128.5, 125.9, 125.5, 63.0, 62.3*, 51.7*, 51.6, 43.8, 42.8*, 28.9, 28.8*, 23.0, 21.6*, 18.1, 17.9*, 15.5, 15.4*.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*w*), 1724 (*vs*), 1603 (*w*), 1434 (*w*), 1266 (*s*), 1203 (*w*), 1046 (*w*), 964 (*w*), 834 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{21}O_3{}^{35}Cl$ $[M]^+$: 332.1174; found: 332.1155.

Methyl (E)-1-chloro-7-ethyl-4-formyl-3,4-dimethyl-3-(prop-1-en-1-yl)-3,4-dihydro naphthalene-2-carboxylate (I.140):



I.139 **I.140**

To sodium hydride (60% dispersion in mineral oil, 32.9 mg, 0.823 mmol, 2.00 equiv) was added a degassed solution of **I.139** (137 mg, 0.412 mmol, 1 equiv) and methyl iodide (0.256 mL, 4.12 mmol, 10.0 equiv) in tetrahydrofuran (5.9 mL) at 0 °C. The solution was allowed to warm to 23 °C and after 5.5 h, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (toluene) to obtain **I.140** (98 mg, 69%) as a light yellow oil.

Analytical data for I.140:

TLC (20% ethyl acetate in hexanes), R_f = 0.45 (UV, CAM, $KMnO_4$).

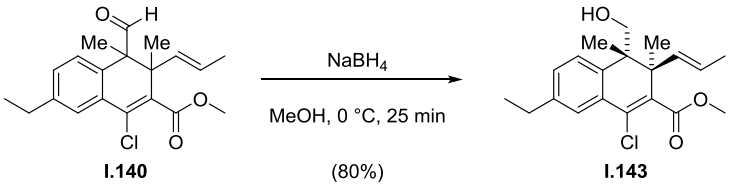
^{1}H NMR (800 MHz, C_6D_6) δ: 9.82 (s, 1H), 7.68 (d, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 7.9, 1.9 Hz, 1H), 5.50 – 5.30 (m, 2H), 3.43 (s, 3H), 2.33 (q, *J* = 7.6 Hz, 2H), 1.35 (s, 3H), 1.34 – 1.30 (m, 3H), 1.24 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (201 MHz, C_6D_6) δ: 199.8, 166.7, 144.5, 141.5, 136.1, 133.2, 131.1, 130.3, 129.9, 127.3, 127.1, 125.9, 56.2, 51.6, 46.2, 28.7, 18.1, 18.0, 15.4, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2969 (*w*), 2362 (*w*), 1731 (*vs*), 1605 (*w*), 1434 (*w*), 1373 (*w*), 1268 (*m*), 1154 (*w*), 1102 (*w*), 1042 (*w*), 968 (*w*), 890 (*w*), 816 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{23}O_3{}^{35}Cl$ $[M]^+$: 346.1330; found: 346.1341.

Methyl (E)-1-chloro-7-ethyl-4-(hydroxymethyl)-3,4-dimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.143):



I.140 **I.143**

To a solution of **I.140** (15.0 mg, 0.0432 mmol, 1 equiv) in methanol (0.4 mL) was added sodium borohydride (2.45 mg, 0.0649 mmol, 1.50 equiv) at 0 °C. After 25 min, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (11% ethyl acetate in hexanes) to obtain **I.143** (12 mg, 80%, major isomer) as a colorless oil.

Analytical data for I.143:

Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk. The relative stereochemistry was assigned by NOE correlations of ***I.147****.*

TLC (20% ethyl acetate in hexanes), R_f = 0.21 (UV, CAM, ANIS, $KMnO_4$).

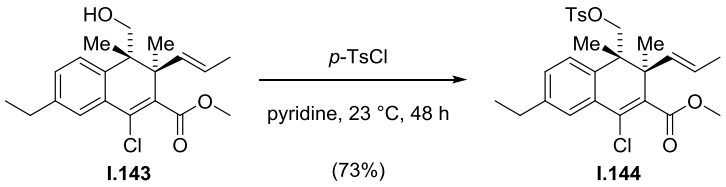
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* = 1.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.9 Hz, 1H), 5.50 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.34 (d, *J* = 15.6 Hz, 1H), 3.90 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.82 (s, 3H), 3.51 (t, *J* = 9.8 Hz, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.60 (dd, *J* = 6.3, 1.5 Hz, 3H), 1.30 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 143.3, 135.9, 131.0, 129.9, 129.2, 127.9*, 127.4*, 126.0, 125.4, 66.0, 52.2, 46.5, 45.8, 29.9, 28.6, 18.3, 16.4*, 16.4, 15.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3430 (*w*), 2964 (*m*), 1731 (*vs*), 1629 (*w*), 1607 (*w*), 1433 (*m*), 1375 (*w*), 1268 (*vs*), 1196 (*w*), 1151 (*m*), 1040 (*s*), 968 (*m*), 890 (*w*), 833 (*w*), 723 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{25}O_3{}^{35}Cl$ $[M]^+$: 348.1487; found: 348.1492.

Methyl (E)-1-chloro-7-ethyl-3,4-dimethyl-3-(prop-1-en-1-yl)-4-((tosyloxy)methyl)-3,4-dihydronaphthalene-2-carboxylate (I.144):



To **I.143** (14.0 mg, 0.0401 mmol, 1 equiv) and *p*-toluenesulfonyl chloride (23.0 mg, 0.120 mmol, 3.00 equiv) was added pyridine (0.3 mL). After stirring for 48 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (15 mL), the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford **I.144** (14.8 mg, 73%) as a colorless oil.

Analytical data for I.144:

Note: Due to severe signal broadening in the NMR spectra some signals are missing or possess inaccurate integrals. Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.

TLC (20% ethyl acetate in hexanes), R_f = 0.31 (UV, ANIS, $KMnO_4$).

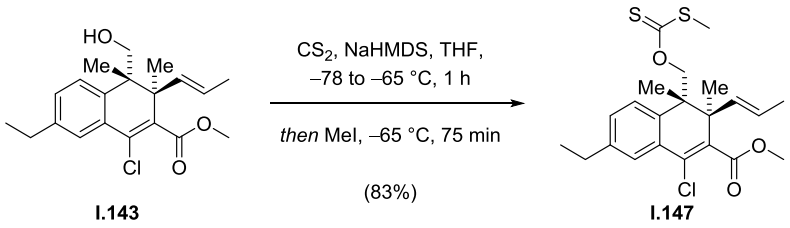
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (s, 1H), 7.21 – 7.10 (m, 4H), 5.44 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.20 (s, 1H), 4.08 (s, 2H), 3.77 (s, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 1.55 (d, *J* = 4.9 Hz, 3H), 1.27 (t, *J* = 7.6 Hz, 6H), 1.16 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.2, 144.5, 143.3, 135.1*, 132.2, 129.8, 129.3, 129.1, 128.1, 127.8, 125.0, 72.6, 52.1, 46.6*, 44.1, 29.9*, 28.6, 21.8, 18.2, 16.7, 15.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 1729 (*s*), 1628 (*w*), 1451 (*w*), 1434 (*w*), 1361 (*m*), 1269 (*m*), 1189 (*s*), 1176 (*vs*), 1097 (*m*), 1041 (*m*), 979 (*s*), 912 (*m*), 830 (*s*), 813 (*s*), 731 (*m*), 666 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{27}H_{31}O_5{}^{35}ClS$ $[M]^+$: 502.1575; found: 502.1574.

Methyl (E)-1-chloro-7-ethyl-3,4-dimethyl-4-((((methylthio)carbonothioyl)oxy)methyl)-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (I.147):



To a solution of **I.143** (12.0 mg, 0.0344 mmol, 1 equiv) in tetrahydrofuran (0.26 mL) was added sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.172 mL, 0.172 mmol, 5.00 equiv) at −78 °C. After 30 min, carbon disulfide (0.0415 mL, 0.688 mmol, 20.0 equiv) was added and the reaction was allowed to warm to −65 °C. After another 30 min, methyl iodide (0.0428 mL, 0.688 mmol, 20.0 equiv) was added and the reaction mixture was stirred for 75 min. Saturated aqueous ammonium chloride solution (15 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **I.147** (12.6 mg, 83%) as a colorless oil.

Analytical data for I.147:

Note: Due to severe signal broadening in the NMR spectra some signals are missing or possess inaccurate integrals. Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.

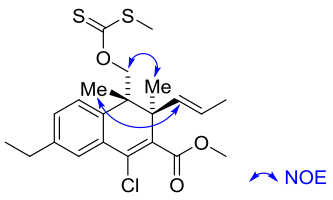
TLC (20% ethyl acetate in hexanes), R_f = 0.50 (UV, ANIS, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 – 7.44 (m, 1H), 7.18 (d, *J* = 1.2 Hz, 2H), 5.64 – 5.37 (m, 2H), 4.75 (s, 2H), 3.81 (s, 3H), 2.67 (q, *J* = 7.8 Hz, 2H), 2.45 (s, 3H), 1.65 (d, *J* = 6.1 Hz, 3H), 1.36 (s, 3H), 1.31 – 1.18 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 215.5, 167.4, 143.4, 137.3*, 135.8*, 130.2, 129.7, 129.5, 128.2, 125.3, 77.0*, 52.1, 47.2*, 44.7, 28.6, 18.9, 18.4, 17.2, 15.5, 10.6*.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2964 (*w*), 1730 (*vs*), 1607 (*w*), 1488 (*w*), 1449 (*w*), 1432 (*m*), 1375 (*w*), 1268 (*s*), 1253 (*s*), 1209 (*s*), 1153 (*m*), 1067 (*vs*), 1041 (*m*), 967 (*m*), 911 (*w*), 832 (*w*), 731 (*w*) cm^{-1}.

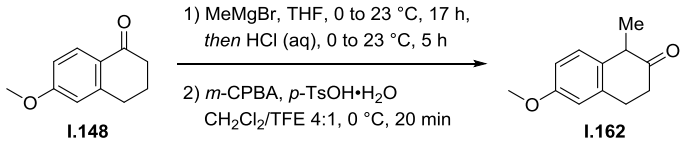
HRMS (EI) calcd for $C_{22}H_{27}O_3{}^{35}ClS_2$ $[M]^+$: 438.1085; found: 438.1077.



The relative stereochemistry was assigned by NOE correlations.

10.2.1.2 Second Generation Approach

6-Methoxy-1-methyl-3,4-dihydronaphthalen-2(1H)-one (I.162):



To **I.148** (10.0 g, 56.7 mmol, 1 equiv) in tetrahydrofuran (100 mL) was added methylmagnesium bromide solution (3 M in diethyl ether, 28.4 mL, 85.1 mmol, 1.50 equiv) at 0 °C. The ice bath was removed after the addition and the reaction mixture was stirred for 17 h. Finally, it was cooled to 0 °C and aqueous hydrochloric acid solution (2 M, 200 mL) was added until pH=2. The reaction was stirred for further 5 h, diluted with water (100 mL) and the layers were separated. The aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was used without further purification. An analytical pure sample of **I.161** was obtained by flash column chromatography on silica gel (2% ethyl acetate in hexanes).

Analytical data for I.161:

TLC (20% ethyl acetate in hexanes), R_f = 0.63 ($KMnO_4$, ANIS).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 8.2 Hz, 1H), 6.88 – 6.62 (m, 2H), 5.73 (ddd, *J* = 6.0, 3.8, 1.6 Hz, 1H), 3.81 (s, 3H), 2.75 (t, *J* = 8.0 Hz, 2H), 2.29 – 2.16 (m, 2H), 2.03 (q, *J* = 1.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.5, 138.3, 131.9, 129.2, 124.0, 123.0, 113.7, 110.9, 55.4, 29.0, 23.3, 19.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2932 (*w*), 1605 (*m*), 1496 (*s*), 1427 (*m*), 1302 (*m*), 1249 (*vs*), 1141 (*s*), 1032 (*s*), 867 (*m*), 819 (*s*), 674 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{14}O$ $[M]^+$: 174.1039; found: 174.1041.

To a solution of crude **I.161** in dichloromethane (283 mL) and trifluoroethanol (71 mL) were added 3-chloroperoxybenzoic acid (75% in water, 16.3 g, 70.9 mmol, 1.25 equiv) and *p*-toluenesulfonic acid monohydrate (13.5 g, 70.9 mmol, 1.25 equiv) subsequently at 0 °C. After stirring for 20 min, saturated aqueous sodium bicarbonate solution (200 mL) and dichloromethane (200 mL) were added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (6% ethyl acetate in hexanes) to obtain **I.162** (4.76 g, 44% over 2 steps) as a yellow oil.

Analytical data for I.162:

TLC (20% ethyl acetate in hexanes), R_f = 0.45 ($KMnO_4$).

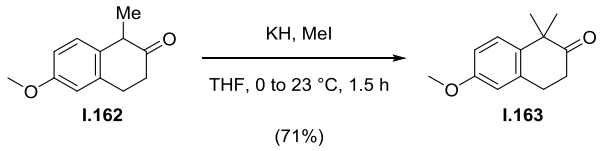
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, *J* = 8.3 Hz, 1H), 6.83 – 6.76 (m, 2H), 3.81 (s, 3H), 3.47 (qd, *J* = 6.9, 0.9 Hz, 1H), 3.15 – 2.91 (m, 2H), 2.62 (dt, *J* = 17.5, 5.9 Hz, 1H), 2.48 (ddd, *J* = 17.5, 9.0, 6.1 Hz, 1H), 1.45 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.5, 158.5, 138.1, 130.1, 127.3, 113.3, 112.3, 55.4, 46.8, 37.3, 28.4, 14.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2937 (*w*), 1713 (*vs*), 1610 (*m*), 1579 (*w*), 1497 (*s*), 1454 (*m*), 1261 (*s*), 1160 (*m*), 1037 (*m*), 864 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0988; found: 190.0994.

6-Methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2(1H)-one (I.163):



To a suspension of freshly washed potassium hydride (4.55 g, 114 mmol, 1.20 equiv) in degassed tetrahydrofuran (40 mL) was added a degassed solution of **I.162** (18.0 g, 94.6 mmol, 1 equiv) in tetrahydrofuran (500 mL) over 25 min at 0 °C. After 20 min, the ice bath was removed and the reaction mixture was stirred at 23 °C. After 1 h, it was cooled back to 0 °C, methyl iodide (11.8 mL, 189 mmol, 2.00 equiv) was added and the ice bath was removed after the addition. After 25 min at 23 °C, the mixture was again cooled to 0 °C, saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (100 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (6% ethyl acetate in hexanes) to afford **I.163** (13.6 g, 71%) as a yellow oil.

Analytical data for I.163:

TLC (20% ethyl acetate in hexanes), R_f = 0.39 ($KMnO_4$, ANIS, UV).

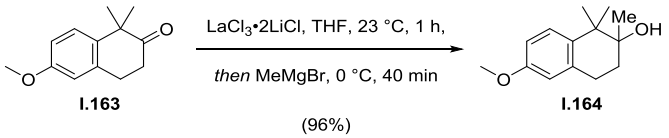
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (s, 1H), 6.84 (ddd, *J* = 8.7, 2.8, 0.7 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 3.83 (s, 3H), 3.09 (t, *J* = 6.9 Hz, 2H), 2.79 – 2.63 (m, 2H), 1.44 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 215.0, 158.1, 136.6, 135.8, 127.4, 113.3, 112.9, 55.4, 47.4, 37.3, 28.9, 27.2 (2C).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*w*), 1709 (*vs*), 1609 (*m*), 1500 (*s*), 1464 (*m*), 1307 (*m*), 1265 (*s*), 1228 (*m*), 1138 (*m*), 1035 (*s*), 814 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1145; found: 204.1133.

6-Methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (I.164):



To a solution of **I.163** (2.74 g, 13.4 mmol, 1 equiv) in tetrahydrofuran (13 mL) was added lanthanum(III) chloride bis(lithium chloride) complex solution[200] (0.3 M in tetrahydrofuran, 44.7 mL, 13.4 mmol, 1 equiv). After 1 h, the solution was cooled to 0 °C and methylmagnesium bromide solution (3 M in diethyl ether, 6.71 mL, 20.1 mmol, 1.50 equiv) was added dropwise over 20 min (syringe pump). After 20 min, saturated aqueous ammonium chloride solution (50 mL) and diethyl ether (50 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to obtain **I.164** (2.83 g, 96%) as a colorless oil.

Analytical data for I.164:

TLC (20% ethyl acetate in hexanes), R_f = 0.23 (ANIS).

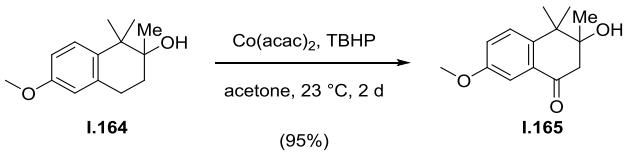
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 8.7 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 2.98 (dt, *J* = 17.6, 7.1 Hz, 1H), 2.81 (dt, *J* = 17.5, 6.8 Hz, 1H), 2.04 – 1.79 (m, 2H), 1.32 (s, 3H), 1.27 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.4, 137.4, 135.5, 128.1, 113.0, 112.8, 73.7, 55.3, 41.5, 32.8, 27.1, 27.0, 25.4, 24.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3470 (*w*), 2969 (*m*), 1608 (*m*), 1499 (*vs*), 1464 (*m*), 1373 (*w*), 1315 (*m*), 1237 (*s*), 1084 (*m*), 1037 (*s*), 911 (*m*), 818 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1458; found: 220.1452.

3-Hydroxy-7-methoxy-3,4,4-trimethyl-3,4-dihydronaphthalen-1(2H)-one (I.165):



To a solution of **I.164** (843 mg, 3.83 mmol, 1 equiv) in dry acetone (7.7 mL) was added cobalt(II) acetylacetonate (197 mg, 0.765 mmol, 0.200 equiv). To the resulting purple suspension was added dropwise *tert*-butyl hydroperoxide (5.5 M in decane, 2.78 mL, 15.3 mmol, 4.00 equiv). After 2 d, saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **I.165** (854 mg, 95%) as a green oil.

Analytical data for I.165:

TLC (20% ethyl acetate in hexanes), R_f = 0.056 (ANIS, UV).

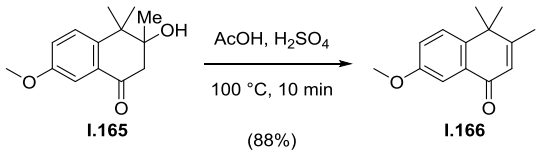
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 3.0 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.84 (s, 3H), 2.89 (s, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 196.8, 158.2, 143.5, 131.8, 127.8, 122.6, 109.1, 75.7, 55.7, 55.6, 50.0, 42.5, 24.7, 24.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3483 (*m*), 2975 (*m*), 1677 (*vs*), 1608 (*s*), 1493 (*s*), 1418 (*m*), 1325 (*s*), 1291 (*vs*), 1262 (*s*), 1087 (*m*), 1032 (*s*), 883 (*w*), 830 (*w*), 705 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{18}O_3$ $[M]^+$: 234.1250; found: 234.1249.

7-Methoxy-3,4,4-trimethylnaphthalen-1(4H)-one (I.166):



A mixture of **I.165** (270 mg, 1.15 mmol, 1 equiv) in acetic acid (11.5 mL) and sulfuric acid (97%, 30 μL) was heated to 100 °C for 10 min. After cooling to 23 °C, the reaction mixture was diluted with water (30 mL) and dichloromethane (50 mL). Sodium bicarbonate was slowly added until pH=7. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to obtain **I.166** (220 mg, 88%) as a yellow solid.

Analytical data for I.166:

TLC (60% ethyl acetate in hexanes), R_f = 0.50 ($KMnO_4$, UV).

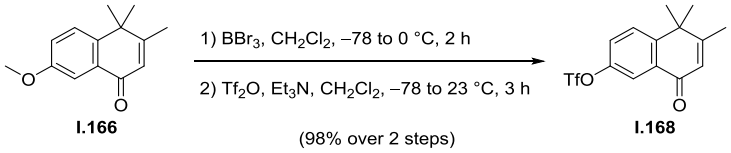
^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 3.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.32 (q, *J* = 1.3 Hz, 1H), 3.88 (s, 3H), 2.14 (d, *J* = 1.3 Hz, 3H), 1.48 (s, 6H).

^{13}C NMR (201 MHz, $CDCl_3$) δ: 184.5, 165.9, 158.2, 144.1, 131.7, 127.9, 126.6, 121.4, 107.6, 55.7, 40.3, 28.7 (2C), 20.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*w*), 1657 (*vs*), 1608 (*m*), 1497 (*s*), 1425 (*s*), 1296 (*s*), 1230 (*w*), 1032 (*w*), 870 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{16}O_2$ $[M]^+$: 216.1145; found: 216.1145.

5,5,6-Trimethyl-8-oxo-5,8-dihydronaphthalen-2-yl trifluoromethanesulfonate (I.168):



To a solution of **I.166** (200 mg, 0.925 mmol, 1 equiv) in dichloromethane (4.6 mL) was added dropwise boron tribromide (1 M, in dichloromethane, 4.62 mL, 4.62 mmol, 5 equiv) at −78 °C. The reaction mixture was allowed to warm to 0 °C over 2 h and methanol (3 mL) was added dropwise. Water (40 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **I.167** was used in the next step without further purification.

To a solution of crude **I.167** in dichloromethane (4.6 mL) was added triethylamine at −78 °C and the mixture was stirred for 5 min before trifluoromethanesulfonic anhydride (0.230 mL, 1.39 mmol, 1.50 equiv) was added over 10 min. The reaction was allowed to warm to 23 °C over 3 h and saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford **I.168** (302 mg, 98% over 2 steps) as a yellow solid.

Analytical data for I.168:

TLC (33% ethyl acetate in hexanes), R_f = 0.26 ($KMnO_4$, UV).

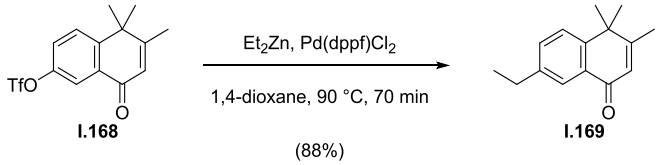
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 2.9 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.36 (t, *J* = 1.3 Hz, 1H), 2.17 (d, *J* = 1.3 Hz, 3H), 1.53 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 182.5, 166.2, 151.1, 148.4, 132.8, 129.2, 126.4, 125.3, 118.9 (q, *J* = 320.3 Hz) 118.8, 40.7, 28.7 (2C), 20.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2980 (*w*), 1660 (*s*), 1579 (*w*), 1486 (*w*), 1421 (*s*), 1314 (*m*), 1290 (*m*), 1204 (*vs*), 1137 (*vs*), 1109 (*m*), 918 (*vs*), 875 (*m*), 841 (*s*), 811 (*s*), 767 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{13}O_4F_3S$ $[M]^+$: 334.0481; found: 334.0490.

7-Ethyl-3,4,4-trimethylnaphthalen-1(4H)-one (I.169):



Note: The reaction setup has to be flame-dried very carefully, since the yield otherwise decreases significantly.

To [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (41.1 mg, 0.0562 mmol, 0.0180 equiv) was added a solution of **I.168** (1.04 g, 3.12 mmol, 1 equiv) in 1,4-dioxane (2.6 mL). The red suspension was cooled to 0 °C and diethylzinc solution (15wt% in toluene, 4.27 mL, 6.25 mmol, 2.00 equiv) was added dropwise. After stirring for 10 min, the yellow solution was heated to 90 °C for 70 min, cooled to 0 °C and treated with methanol (5 mL). Water (15 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with aqueous hydrogen chloride solution (2 M, 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to obtain **I.169** (590 mg, 88%) as a yellow oil.

Analytical data for I.169:

TLC (20% ethyl acetate in hexanes), R_f = 0.35 ($KMnO_4$, UV).

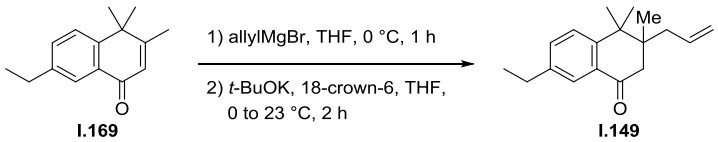
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.42 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.32 (d, *J* = 1.5 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.13 (d, *J* = 1.1 Hz, 3H), 1.49 (s, 6H), 1.27 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 184.9, 165.6, 148.8, 142.6, 132.5, 130.4, 126.8, 126.5, 125.2, 40.4, 28.7, 28.5, 20.3, 15.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 2873 (*w*), 1657 (*vs*), 1610 (*m*), 1462 (*w*), 1427 (*m*), 1307 (*m*), 1270 (*w*), 1117 (*w*), 1011 (*w*), 876 (*m*), 837 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{18}O_2$ $[M]^+$: 214.1352; found: 214.1351.

3-Allyl-7-ethyl-3,4,4-trimethyl-3,4-dihydronaphthalen-1(2H)-one (I.149):



I.169 I.149

(38% over 2 steps)

To a solution of **I.169** (590 mg, 2.75 mmol, 1 equiv) in tetrahydrofuran (5.5 mL) was added dropwise allylmagnesium bromide solution (1 M in diethyl ether, 4.13 mL, 4.13 mmol, 1.50 equiv) at 0 °C. After 1 h, it was cooled back to 0 °C and saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **I.170** was used without further purification.

A mixture of 18-crown-6 (1.45 g, 5.50 mmol, 2.00 equiv) and potassium *tert*-butoxide (617 mg, 5.50 mmol, 2.00 equiv) in tetrahydrofuran (46 mL) was stirred at 0 °C for 1 h. A solution of crude **I.170** in tetrahydrofuran (10 mL) was added over 10 min and after complete addition, the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (40 mL) and dichloromethane (40 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to obtain **I.149** (270 mg, 38% over 2 steps) as a yellow oil.

Analytical data for I.149:

TLC (20% ethyl acetate in hexanes), R_f = 0.59 ($KMnO_4$, UV).

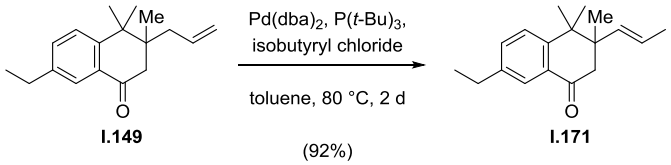
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (s, 1H), 7.38 (s, 2H), 5.78 (ddt, *J* = 15.0, 10.1, 7.5 Hz, 1H), 5.08 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.60 (s, 2H), 2.17 – 2.13 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.4, 149.9, 142.1, 134.5, 134.2, 131.3, 126.4, 125.7, 118.6, 46.1, 41.2, 40.9, 40.4, 28.3, 20.9, 15.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2969 (*s*), 1683 (*vs*), 1639 (*w*), 1611 (*m*), 1456 (*m*), 1376 (*m*), 1296 (*m*), 1263 (*m*), 1093 (*m*), 999 (*m*), 913 (*m*), 835 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{24}O$ $[M]^+$: 256.1822; found: 256.1820.

(E)-7-Ethyl-3,4,4-trimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (I.171):



To bis(dibenzylidenacetone)palladium(0) (66.1 mg, 0.115 mmol, 10.0 mol%) was added subsequently a solution of **I.149** (295 mg, 1.15 mmol, 1 equiv) in degassed toluene (3.3 mL), tri-*t*-butylphosphine (1 M in toluene, 0.115 mL, 0.115 mmol, 10.0 mol%) and isobutyryl chloride (0.078M in degassed toluene, 1.47 mL, 0.115 mmol, 10.0 mol%). The reaction mixture was heated to 80 °C for 2 d, diluted afterwards with ethyl acetate (30 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **I.171** (272 mg, 92%) as a yellow oil.

Analytical data for I.171:

TLC (20% ethyl acetate in hexanes), R_f = 0.58 ($KMnO_4$, UV).

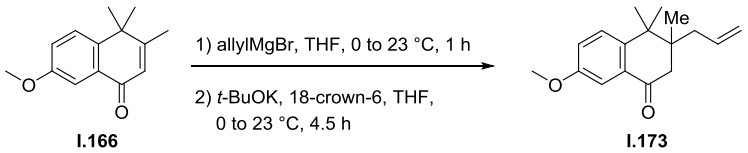
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 1.9 Hz, 1H), 7.40 – 7.33 (m, 2H), 5.61 (d, *J* = 15.7 Hz, 1H), 5.47 (dq, *J* = 15.6, 6.2 Hz, 1H), 2.83 (d, *J* = 17.3 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.53 (d, *J* = 17.4 Hz, 1H), 1.67 (d, *J* = 6.2 Hz, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.6, 149.7, 142.0, 135.9, 134.1, 130.9, 126.4, 125.8, 124.5, 48.1, 43.5, 40.6, 28.3, 26.8, 24.5, 21.7, 18.5, 15.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*m*), 2936 (*w*), 1683 (*vs*), 1611 (*w*), 1491 (*w*), 1452 (*w*), 1376 (*w*), 1290 (*w*), 1264 (*w*), 1096 (*w*), 975 (*w*), 834 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{24}O$ $[M]^+$: 256.1822; found: 256.1821.

3-Allyl-7-methoxy-3,4,4-trimethyl-3,4-dihydronaphthalen-1(2H)-one (I.173):



I.166 **I.173**

(77% over 2 steps)

To a solution of **I.166** (5.75 g, 26.6 mmol, 1 equiv) in tetrahydrofuran (53 mL) was added allylmagnesium bromide solution (1 M in diethyl ether, 39.9 mL, 39.9 mmol, 1.50 equiv) over 30 min (syringe pump) at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 1 h, it was cooled back to 0 °C and saturated aqueous sodium bicarbonate solution (60 mL) and dichloromethane (60 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **I.172** was used without further purification.

A mixture of 18-crown-6 (14.1 g, 53.2 mmol, 2.00 equiv) and potassium *tert*-butoxide (5.97 g, 53.2 mmol, 2.00 equiv) in tetrahydrofuran (445 mL) was stirred at 0 °C for 1 h. A solution of crude **I.172** in tetrahydrofuran (95 mL) was added over 10 min and after the addition, the reaction mixture was allowed to warm to 23 °C. After 4.5 h, saturated aqueous sodium bicarbonate solution (200 mL) and dichloromethane (200 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **I.173** (5.31 g, 77% over 2 steps) as a dark orange oil.

Analytical data for I.173:

Note: Severe signal broadening was observed in the NMR spectra recorded at room temperature. Better resolved spectra could be obtained at 50 °C; however, some carbon atoms are still not visible in the ^{13}C NMR spectrum.

TLC (20% ethyl acetate in hexanes), R_f = 0.50 ($KMnO_4$, UV).

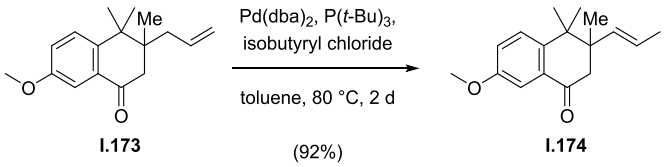
^{1}H NMR (400 MHz, 50 °C, $CDCl_3$) δ: 7.51 (d, *J* = 3.0 Hz, 1H), 7.37 (dd, *J* = 8.7, 0.4 Hz, 1H), 7.11 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.79 (ddt, *J* = 17.3, 10.1, 7.5 Hz, 1H), 5.08 (ddt, *J* = 10.1, 1.9, 0.9 Hz, 1H), 4.99 (dd, *J* = 16.9, 1.6 Hz, 1H), 3.85 (s, 3H), 2.61 (d, *J* = 4.6 Hz, 2H), 2.27 – 2.08 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, 50 °C, $CDCl_3$) δ: 197.5, 157.9, 144.9, 134.4, 132.4, 127.5, 122.1, 118.2, 108.9, 55.4, 46.1, 40.9, 40.4, 29.6, 25.6*, 24.6*, 20.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2973 (*m*), 2360 (*w*), 1684 (*vs*), 1608 (*m*), 1492 (*s*), 1417 (*w*), 1324 (*m*), 1290 (*m*), 1232 (*m*), 1033 (*m*), 828 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1614; found: 258.1612.

(E)-7-Methoxy-3,4,4-trimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (I.174):



I.173 I.174

To bis(dibenzylidenacetone)palladium(0) (5.34 mg, 0.00929 mmol, 10.0 mol%) was added subsequently a solution of **I.173** (24 mg, 0.0929 mmol, 1 equiv) in degassed toluene (0.34 mL), tri-*t*-butylphosphine (1 M in toluene, 9.29 µL, 0.00929 mmol, 10.0 mol%) and isobutyryl chloride (0.078 M in degassed toluene, 0.119 mL, 0.00929 mmol, 10.0 mol%). The reaction mixture was heated to 80 °C for 2 d, diluted afterwards with ethyl acetate (15 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate and 1% acetic acid in hexanes) to afford **I.174** (22 mg, 92%) as a yellow oil.

Analytical data for I.174:

Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.

TLC (20% ethyl acetate in hexanes), R_f = 0.50 ($KMnO_4$, UV).

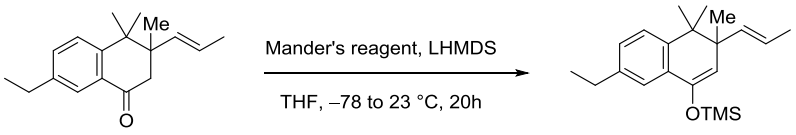
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 3.0 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.11 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.61 (d, *J* = 15.7 Hz, 1H), 5.47 (dq, *J* = 15.6, 6.2 Hz, 1H), 3.84 (s, 3H), 2.83 (d, *J* = 16.9 Hz, 1H), 2.55 (d, *J* = 17.4 Hz, 1H), 1.67 (d, *J* = 6.1 Hz, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.2, 157.8, 144.9, 135.8, 131.9, 127.8, 124.5, 122.3, 108.8, 55.6, 48.0, 43.6, 40.4, 27.0*, 24.8*, 21.7, 18.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (*m*), 1681 (*vs*), 1607 (*m*), 1490 (*s*), 1416 (*m*), 1376 (*w*), 1323 (*m*), 1283 (*s*), 1231 (*s*), 1032 (*s*), 975 (*m*), 828 (*m*), 703 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1614; found: 258.1607.

(E)-((7-Ethyl-3,4,4-trimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane (I.176):



I.171 **I.176**

To a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 58.5 μL, 0.0585 mmol, 1.50 equiv) was added **I.171** (10.0 mg, 0.0390 mmol, 1 equiv) in tetrahydrofuran (0.3 mL) at −78 °C. Methyl cyanoformate (6.19 μL, 0.0780 mmol, 2.00 equiv) was added after stirring for 1.5 h and the reaction was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes) to yield **I.176** (4.1 mg, 32%) as a colorless oil.

Analytical data for I.176:

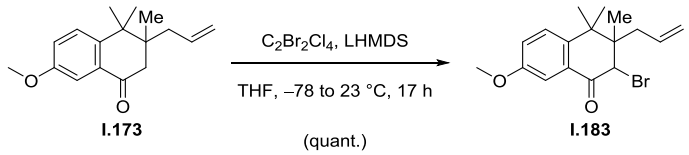
TLC (20% ethyl acetate in hexanes), R_f = 0.73 (UV, CAM, $KMnO_4$)

^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.15 (d, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8, 2.0 Hz, 1H), 5.50 (d, *J* = 15.8 Hz, 1H), 5.45 (dq, *J* = 15.5, 5.9 Hz, 1H), 4.86 (s, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.65 (d, *J* = 5.6 Hz, 3H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.06 (s, 3H), 0.27 (s, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) δ: 146.1, 143.2, 141.4, 135.9, 131.3, 127.5, 124.3, 123.1, 121.6, 115.6, 44.0, 40.4, 28.6, 24.3, 23.5, 20.4, 18.3, 15.5, 0.5.

HRMS (EI) calcd for $C_{21}H_{32}O_1{}^{28}Si$ $[M]^+$: 328.2217; found: 328.2217.

3-Allyl-2-bromo-7-methoxy-3,4,4-trimethyl-3,4-dihydronaphthalen-1(2H)-one (I.183):



To a solution of **I.173** (100 mg, 0.387 mmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.581 mL, 0.581 mmol, 1.50 equiv) at −78 °C. The mixture was stirred for 30 min and a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (189 mg, 0.581 mmol, 1.50 equiv) in tetrahydrofuran (2.5 mL) was added. The reaction was allowed to warm to 23 °C over 17 h and a saturated aqueous ammonium chloride solution (15 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **I.183** (130 mg, quant.) as a light yellow oil.

Note: Since the reaction afforded an inseparable mixture of isomers no NMR spectra of purified ***I.183*** *are reported.*

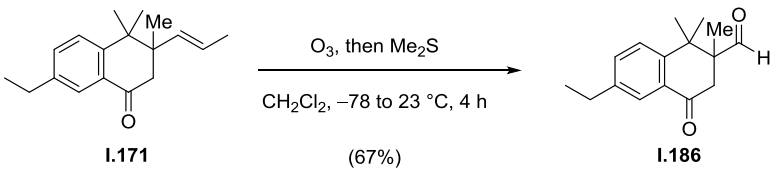
Analytical data for I.183:

TLC (14% ethyl acetate in hexanes), R_f = 0.39 (ANIS, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3076 (*w*), 2978 (*m*), 2837 (*w*), 1699 (*s*), 1609 (*s*), 1496 (*vs*), 1464 (*m*), 1333 (*s*), 1287 (*vs*), 1247 (*s*), 1176 (*w*), 1031 (*s*), 920 (*m*), 832 (*m*), 720 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{20}O_2{}^{79}Br$ $[M-H]^-$: 335.0652; found: 335.0646.

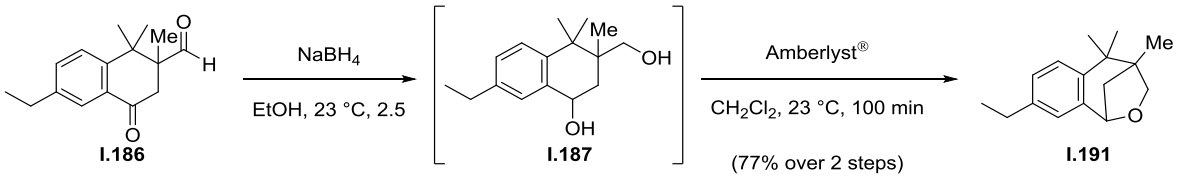
6-Ethyl-1,1,2-trimethyl-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (I.186):



A solution of **I.171** (154 mg, 0.601 mmol, 1 equiv) in dichloromethane (25 mL) was cooled to −78 °C and a stream of ozone was bubbled through the reaction mixture for 10 min. Afterwards, a stream of oxygen was bubbled through the blue reaction mixture for 5 min. After

10 min, dimethyl sulfide (0.222 mL, 3.00 mmol, 5.00 equiv) was added. The reaction mixture was allowed to warm to 23 °C over 4 h, diluted with dichloromethane (20 mL) and concentrated. The crude product was purified by flash column chromatography on silica gel (14.3% ethyl acetate in hexanes) to provide **I.186** (97.6 mg, 67%) as a colorless oil. The product was immediately used for the next reaction due to its instability. For the same reason it was not possible to obtain clean analytical data, since the product started to decompose immediately after the purification.

8-Ethyl-4,5,5-trimethyl-1,3,4,5-tetrahydro-1,4-methanobenzo[c]oxepine (I.191):



To a solution of **I.186** (9.00 mg, 0.0368 mmol, 1 equiv) in ethanol (1 mL) was added sodium borohydride (5.57 mg, 0.0147 mmol, 4.00 equiv). After 2.5 h, water (10 mL) and ethyl acetate (10 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product **I.187** was used without further purification.

To a solution of crude **I.187** in dichloromethane (5 mL) was added Amberlyst® (23.1 mg, 0.0736 mmol, 2.00 equiv). After 100 min, the reaction mixture was filtered through sodium sulfate, the filtercake was thoroughly rinsed with dichloromethane and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **I.191** (6.5 mg, 77%) as a colorless oil.

Analytical data for I.191:

TLC (25% ethyl acetate in hexanes), R_f = 31 (CAM).

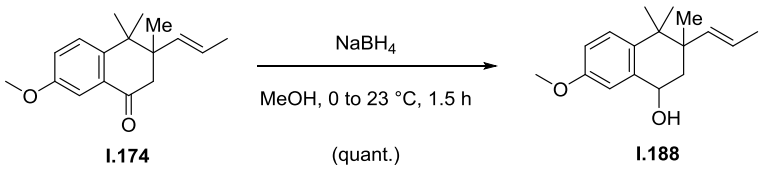
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, *J* = 4.6 Hz, 1H), 7.10 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 4.75 (d, *J* = 5.0 Hz, 1H), 4.08 (d, *J* = 8.8 Hz, 1H), 3.48 (d, *J* = 8.8 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.24 (d, *J* = 11.5 Hz, 1H), 1.84 (dd, *J* = 11.5, 5.1 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 1.26 – 1.17 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.2, 142.0, 138.2, 128.1, 127.4, 126.1, 79.0, 75.1, 46.8, 42.1, 40.0, 29.4, 28.3, 24.0, 19.7, 15.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 2934 (*m*), 2878 (*w*), 1497 (*w*), 1452 (*m*), 1374 (*w*), 1260 (*w*), 1242 (*w*), 1152 (*w*), 1073 (*w*), 1034 (*vs*), 962 (*m*), 909 (*m*), 884 (*m*), 829 (*m*), 731 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{22}O$ $[M]^+$: 230.1665; found: 230.1662.

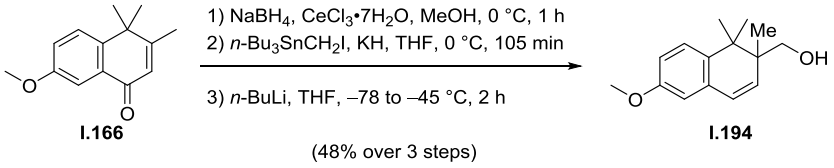
(E)-7-Methoxy-3,4,4-trimethyl-3-(prop-1-en-1-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (I.188):



I.174 I.188

To a solution of **I.174** (35.0 mg, 0.135 mmol, 1 equiv) in methanol (0.5 mL) was added sodium borohydride (10.2 mg, 0.271 mmol, 2.00 equiv) at 0 °C. The mixture was allowed to warm to 23 °C and after 1.5 h, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product **I.188** was filtered through a short plug of silica gel and used without further purification.

(6-Methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methanol (I:194):



I.166 I.194

To a solution of **I.166** (870 mg, 4.02 mmol, 1 equiv) in methanol (34 mL) were added cerium(III) chloride heptahydrate (1.65 g, 4.42 mmol, 1.10 equiv) and sodium borohydride (228 mg, 6.03 mmol, 1.50 equiv) respectively at 0 °C. After 1 h, the mixture was diluted with pH7 buffer solution (20 mL) and dichloromethane (20 mL).The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude

product was used immediately without further purification. *Note: The product is very sensitive toward acidic conditions wand was found to undergo facile elimination. Therefore it was used immediately in the next step.*

To washed potassium hydride (242 mg, 6.03 mmol, 1.50 equiv) was added a solution of the crude alcohol in tetrahydrofuran (60 mL) at 0 °C. After 10 min, a solution of tributyl(iodomethyl)stannane[201] (1.91 g, 4.42 mmol, 1.10 equiv) in tetrahydrofuran (15 mL) was added. After 105 min, the mixture was diluted with pH7 buffer solution (30 mL) and dichloromethane (30 mL).The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product **I.193** was used immediately without further purification.

To a solution of crude **I.193** in tetrahydrofuran (80 mL) was added *n*-butyllithium (2.51 M in hexanes, 2.08 mL, 5.23 mmol, 1.30 equiv) dropwise over 5 min at −78 °C. The reaction was allowed to warm to −45 °C over 2 h and was diluted with saturated aqueous ammonium chloride solution (30 mL) and water (20 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to obtain **I.194** (250 mg, 48% over 3 steps) as a yellow oil.

Analytical data for I.194:

TLC (25% ethyl acetate in hexanes), R_f = 0.26 ($KMnO_4$, CAM, UV).

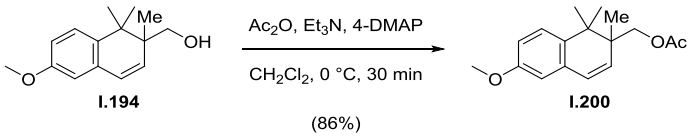
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H), 5.68 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.39 (d, *J* = 10.8 Hz, 1H), 1.29 (s, 4H), 1.13 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.9, 137.3, 135.5, 133.3, 127.3, 125.2, 112.9, 112.2, 67.8, 55.3, 43.0, 38.6, 25.8, 21.6, 17.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3409 (*m*), 2969 (*m*), 2877 (*w*), 1746 (*w*), 1602 (*m*), 1490 (*m*), 1309 (*m*), 1259 (*vs*), 1154 (*w*), 1035 (*vs*), 777 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{20}O_2$ $[M]^+$: 232.1458; found: 232.1458.

(6-Methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methyl acetate (I.200):



To a solution of **I.194** (10.0 mg, 0.0430 mmol, 1 equiv) in dichloromethane (0.43 mL) were added triethylamine (17.9 µL, 0.129 mmol, 3.00 equiv), acetic anhydride (10.5 µl, 0.112 mmol, 2.60 equiv) and 4-dimethylaminopyridine (0.526 mg, 0.00430 mmol, 0.100 equiv) at 0 °C. After 30 min, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **I.200** (10.2 mg, 86%) as a colorless oil.

Analytical data for I.200:

TLC (20% ethyl acetate in hexanes), R_f = 0.31 (UV, CAM).

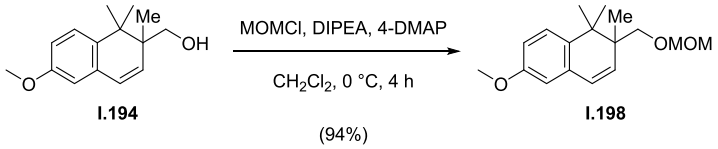
^{1}H NMR (599 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.3 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 6.39 (d, *J* = 9.7 Hz, 1H), 5.67 (d, *J* = 9.5 Hz, 1H), 4.01 (q, *J* = 10.7 Hz, 2H), 3.78 (s, 3H), 1.94 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 171.4, 158.0, 136.8, 135.1, 133.2, 126.7, 125.2, 112.8, 112.2, 68.6, 55.4, 41.4, 39.0, 24.7, 22.5, 21.0, 17.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 1738 (*s*), 1603 (*m*), 1491 (*m*), 1375 (*m*), 1260 (*s*), 1237 (*vs*), 1154 (*m*), 1034 (*s*), 856 (*s*), 777 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{22}O_3$ $[M]^+$: 274.1563; found: 274.1564.

6-Methoxy-2-((methoxymethoxy)methyl)-1,1,2-trimethyl-1,2-dihydronaphthalene (I.198):



To a solution of **I.194** (20.0 mg, 0.0861 mmol, 1 equiv) in dichloromethane (0.43 mL) were added *N*,*N*-diisopropylethylamine (59.6 μL, 0.344 mmol, 4.00 equiv), 4-dimethylaminopyridine (1.05 mg, 0.008641 mmol, 0.100 equiv) and chloromethyl methyl ether (22.9 μL, 0.301 mmol, 3.50 equiv) respectively at 0 °C. The reaction mixture was allowed to warm to 23 °C and after 4 h, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **I.198** (22.3 mg, 94%) as a colorless oil.

Analytical data for I.198:

TLC (20% ethyl acetate in hexanes), R_f = 0.43 (UV, $KMnO_4$).

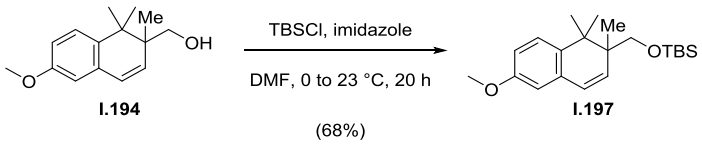
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.77 (d, *J* = 9.6 Hz, 1H), 4.59 – 4.52 (m, 2H), 3.79 (s, 3H), 3.45 (s, 2H), 3.32 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.0, 137.0, 136.6, 133.5, 125.7, 125.2, 112.5, 112.1, 97.0, 72.3, 55.3, 55.3, 42.0, 39.1, 24.3, 22.9, 17.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*w*), 2931 (*w*), 1602 (*w*), 1464 (*w*), 1309 (*w*), 1260 (*m*), 1149 (*m*), 1105 (*m*), 1037 (*vs*), 916 (*w*), 854 (*w*), 776 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{24}O_3$ $[M]^+$: 276.1720; found: 276.1715.

***tert*-Butyl((6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)dimethyl-silane (I.197):**



To a solution of **I.194** (20.0 mg, 0.0861 mmol, 1 equiv) in dimethylformamide (0.21 mL) were added imidazole (11.7 mg, 0.172 mmol, 2.00 equiv) and *tert*-butyldimethylsilyl chloride (19.5 mg, 0.129 mmol, 1.50 equiv) at 0 °C and the reaction was allowed to warm to 23 °C. After 20 h, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **I.197** (20.2 mg, 68%) as a colorless oil.

Analytical data for I.197:

TLC (20% ethyl acetate in hexanes), R_f = 0.68 (UV, CAM).

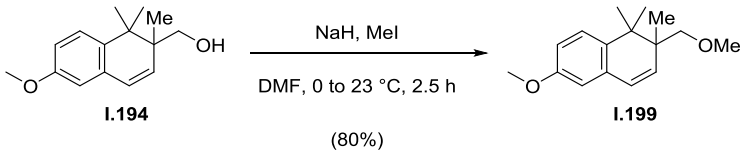
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 9.6 Hz, 1H), 5.71 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 1.21 (d, *J* = 3.6 Hz, 6H), 1.02 (s, 3H), 0.86 (s, 9H), -0.03 (d, *J* = 2.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.8, 137.5, 137.1, 133.7, 125.6, 125.1, 112.4, 111.9, 67.0, 55.3, 43.1, 39.0, 26.0, 24.5, 23.2, 18.4, 17.6, -5.4, -5.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*m*), 2928 (*m*), 2855 (*w*), 1602 (*w*), 1463 (*m*), 1360 (*w*), 1309 (*w*), 1259 (*s*), 1072 (*s*), 1038 (*s*), 1005 (*m*), 849 (*vs*), 835 (*vs*), 773 (*vs*), 668 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{34}O_2Si$ $[M]^+$: 346.2323; found: 346.2322.

6-Methoxy-2-(methoxymethyl)-1,1,2-trimethyl-1,2-dihydronaphthalene (I.199):



To a solution of **I.194** (20.0 mg, 0.0861 mmol, 1 equiv) in dimethylformamide (0.43 mL) was added sodium hydride (60% dispersion in mineral oil, 6.89 mg, 0.172 mmol, 2.00 equiv) at 0 °C. After 15 min, methyl iodide (9.65 mL, 0.155 mmol, 1.80 equiv) was added and the mixture was allowed to warm to 23 °C over 2.5 h. Saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **I.199** (17 mg, 80%) as a colorless oil.

Analytical data for I.199:

TLC (20% ethyl acetate in hexanes), R_f = 0.61 (UV, CAM).

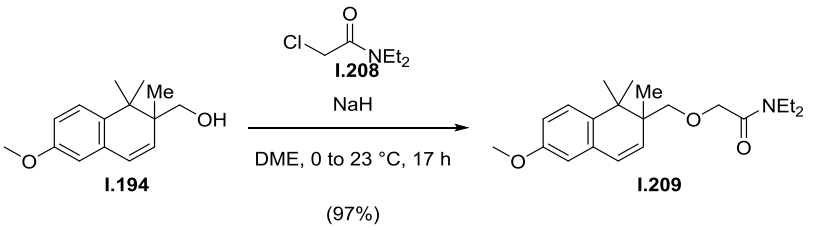
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.75 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.33 – 3.22 (m, 5H), 1.22 (s, 3H), 1.18 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.9, 137.0, 136.9, 133.5, 125.5, 125.2, 112.5, 112.0, 77.4, 59.5, 55.3, 42.2, 39.1, 24.4, 22.8, 17.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (*m*), 2932 (*m*), 1886 (*m*), 1602 (*m*), 1572 (*m*), 1489 (*m*), 1464 (*m*), 1361 (*w*), 1309 (*m*), 1282 (*m*), 1261 (*vs*), 1194 (*m*), 1154 (*m*), 1105 (*vs*), 1089 (*s*), 1037 (*s*), 982 (*w*), 871 (*w*), 777 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{22}O_2$ $[M]^+$: 246.1620; found: 246.1614.

***N,N*-Diethyl-2-((6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)acetamide (I.209):**



(97%)

To a solution of **I.194** (100 mg, 0.430 mmol, 1 equiv) in 1,2-dimethoxyethane (2.2 mL) was added sodium hydride (60% dispersion in mineral oil, 51.6 mg, 1.29 mmol, 3.00 equiv) at 0 °C and after 20 min 2-chloro-*N*,*N*-diethylacetamide (**I.208**) (88.7 µL, 0.646 mmol, 1.50 equiv). The reaction was allowed to warm slowly to 23 °C over 17 h and diluted with saturated aqueous ammonium chloride solution (10 mL) and water (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **I.209** (144 mg, 97%) as a colorless oil.

Analytical data for I.209:

TLC (33% ethyl acetate in hexanes), R_f = 0.17 (UV, CAM).

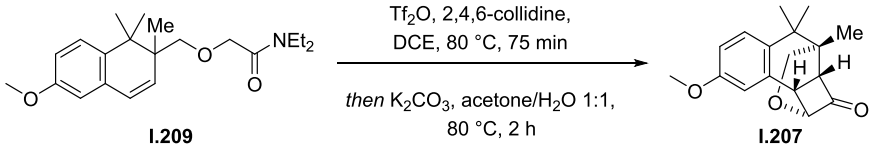
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 6.34 (d, *J* = 9.6 Hz, 1H), 5.78 (d, *J* = 9.7 Hz, 1H), 4.04 (q, *J* = 13.2 Hz, 2H), 3.78 (s, 3H), 3.47 – 3.25 (m, 6H), 1.26 – 1.04 (m, 15H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.5, 157.9, 136.9, 136.7, 133.4, 125.6, 125.2, 112.4, 112.0, 76.0, 71.3, 55.3, 42.3, 41.1, 39.8, 39.0, 24.3, 22.8, 17.9, 14.4, 12.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 2935 (*m*), 2874 (*w*), 1645 (*vs*), 1603 (*m*), 1572 (*w*), 1464 (*m*), 1431 (*m*), 1381 (*w*), 1362 (*w*), 1309 (*m*), 1261 (*vs*), 1222 (*m*), 1153 (*m*), 1102 (*m*), 1088 (*m*), 1036 (*m*), 947 (*w*), 871 (*w*), 791 (*w*), 779 (*w*), 734 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{31}O_3N$ $[M]^+$: 345.2298; found: 345.2295.

7-Methoxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-1,3-(epoxymethano)cyclobuta[a]-naphthalen-2(1H)-one (I.207):



To a solution of **I.209** (60.0 mg, 0.174 mmol, 1 equiv) in 1,2-dichloroethane (6 mL) were added 2,4,6-collidine (11.7 μL, 0.868 mmol, 5.00 equiv) and trifluoromethanesulfonic anhydride (1 M in dichloromethane, 0.868 mL, 0.868 mmol, 5.00 equiv) and the reaction mixture was heated to 80 °C. After 75 min, potassium carbonate (120 mg, 0.868 mmol, 5.00 equiv), acetone (6 mL) and water (6 mL) were added and the mixture was heated to 70 °C. After 2 h, aqueous hydrochloric acid solution (2 M, 20 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to yield **I.207** (33 mg, 70%) as a yellow oil.

Analytical data for I.207:

TLC (25% ethyl acetate in hexanes), R_f = 0.41 (CAM, ANIS, $KMnO_4$).

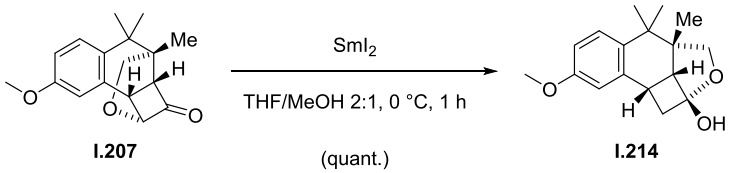
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 4.66 (dd, *J* = 6.7, 4.3 Hz, 1H), 4.05 (dt, *J* = 12.1, 0.9 Hz, 1H), 3.80 (s, 3H), 3.50 (d, *J* = 12.1 Hz, 1H), 3.41 (tt, *J* = 6.1, 0.7 Hz, 1H), 3.27 (dd, *J* = 6.0, 4.3 Hz, 1H), 1.41 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 204.8, 158.0, 139.1, 130.3, 126.3, 113.7, 113.6, 93.0, 71.9, 64.2, 55.3, 45.9, 38.1, 35.8, 30.9, 21.5, 20.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*m*), 2865 (*w*), 1780 (*vs*), 1610 (*m*), 1501 (*m*), 1465 (*m*), 1316 (*w*), 1260 (*m*), 1249 (*m*), 1153 (*w*), 1053 (*m*), 1037 (*m*), 908 (*m*), 818 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1407; found: 272.1406.

7-Methoxy-3a,4,4-trimethyl-3,3a,4,8b-tetrahydro-1H-benzo[f]cyclobuta[cd]isobenzofuran-1a(1a1H)-ol (I.214):



I.207 I.214

To a degassed solution of **I.207** (12.0 mg, 0.0441 mmol, 1 equiv) in tetrahydrofuran (1.2 mL) and methanol (0.6 mL) was added dropwise a solution of samarium(II) iodide (0.1 M in tetrahydrofuran, 3.52 mL, 0.352 mmol, 8.00 equiv) at 0 °C. After 1 h, water (10 mL) and aqueous hydrochloric acid solution (2 M, 10 mL) were added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **I.214** (12 mg, quant.) as a colorless oil.

Analytical data for I.214:

TLC (33% ethyl acetate in hexanes), R_f = 0.26 (CAM).

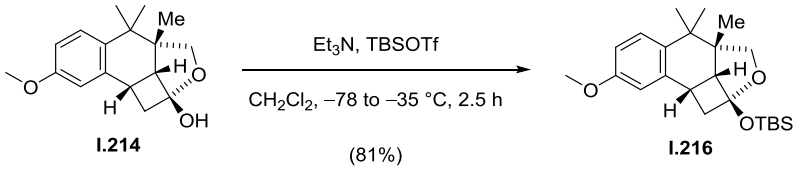
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (d, *J* = 8.8 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 3.68 (d, *J* = 8.9 Hz, 1H), 3.51 (d, *J* = 8.9 Hz, 1H), 3.34 (td, *J* = 10.4, 5.0 Hz, 1H), 3.05 (ddd, *J* = 12.9, 11.2, 1.7 Hz, 1H), 2.75 – 2.66 (m, 2H), 2.23 (dd, *J* = 13.0, 5.1 Hz, 1H), 1.28 (s, 6H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.8, 139.4, 136.8, 126.1, 112.8, 112.3, 106.4, 76.7, 55.3, 53.6, 46.6, 44.2, 37.9, 29.5, 23.6, 22.2, 21.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3391 (*w*), 2971 (*m*), 1608 (*m*), 1575 (*w*), 1502 (*m*), 1424 (*w*), 1364 (*w*), 1284 (*s*), 1254 (s), 1216 (*w*), 1158 (*m*), 1125 (*w*), 1037 (*vs*), 867 (*m*), 815 (*m*), 728 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{22}O_3$ $[M]^+$: 274.1563; found: 274.1572.

***tert*-Butyl((7-methoxy-3a,4,4-trimethyl-3,3a,4,8b-tetrahydro-1H-benzo[f]cyclobuta[cd] isobenzofuran-1a(1a1H)-yl)oxy)dimethylsilane (I.216):**



To a solution of **I.214** (4.70 mg, 0.0171 mmol, 1 equiv) in dichloromethane (1.1 mL) were added triethylamine (47.6 μL, 0.343 mmol, 20.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (39.3 μL, 0.171 mmol, 10.0 equiv) at −78 °C and the reaction was allowed to warm to −35 °C over 2.5 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL), the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **I.216** (5.4 mg, 81%) as a colorless oil.

Analytical data for I.216:

TLC (33% ethyl acetate in hexanes), R_f = 0.75 (CAM).

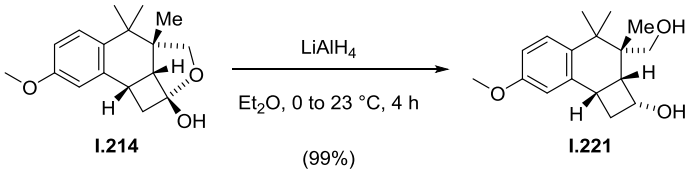
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2 (d, *J* = 8.7 Hz, 1H), 6.7 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.6 (d, *J* = 2.8 Hz, 1H), 3.8 (s, 3H), 3.6 (d, *J* = 8.6 Hz, 1H), 3.5 (d, *J* = 8.7 Hz, 1H), 3.3 (td, *J* = 10.0, 4.0 Hz, 1H), 2.9 (t, *J* = 11.3 Hz, 1H), 2.8 (d, *J* = 9.4 Hz, 1H), 2.3 (dd, *J* = 12.0, 4.0 Hz, 1H), 1.3 (s, 6H), 1.0 (s, 3H), 0.9 (s, 9H), 0.1 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.8, 140.4, 137.2, 125.8, 112.9, 111.8, 107.4, 78.5, 56.2, 55.2, 47.8, 45.6, 38.5, 28.8, 25.9, 25.3, 22.3, 22.0, 17.9, -3.2, -3.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*s*), 2930 (*s*), 2857 (*m*), 1700 (*w*), 1608 (*w*), 1576 (*w*), 1499 (*m*), 1472 (*m*), 1464 (*m*), 1390 (*m*), 1290 (*s*), 1253 (*s*), 1214 (*w*), 1160 (*m*), 1140 (*m*), 1101 (*m*), 1040 (*vs*), 962 (*m*), 902 (*m*), 836 (*s*), 780 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{23}H_{36}O_3Si$ $[M]^+$: 388.2428; found: 388.2427.

3-(Hydroxymethyl)-7-methoxy-3,4,4-trimethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a] naphthalen-2-ol (I.221):



To a solution of **I.214** (12.0 mg, 0.0437 mmol, 1 equiv) in diethyl ether (3 mL) was added lithium aluminum hydride (16.6 mg, 0.437 mmol, 10.0 equiv) at 0 °C and the reaction mixture was allowed to warm slowly to 23 °C. After 4 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (15 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **I.221** (12 mg, 99%, d.r. = 30:1) as a colorless oil.

Analytical data for I.221:

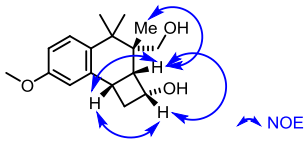
TLC (50% ethyl acetate in hexanes), R_f = 0.20 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09 (d, *J* = 8.5 Hz, 1H), 6.66 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 4.52 (dt, *J* = 9.7, 8.1 Hz, 1H), 3.77 (s, 3H), 3.55 – 3.44 (m, 2H), 3.35 (s, 2H), 3.12 (q, *J* = 8.9 Hz, 1H), 3.03 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.90 (dtd, *J* = 11.3, 8.0, 3.3 Hz, 1H), 2.00 (q, *J* = 10.1 Hz, 1H), 1.31 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.2, 140.7, 137.0, 124.9, 112.3, 111.1, 65.5, 65.1, 55.3, 49.8, 42.9, 41.1, 40.1, 27.9, 27.3, 21.5, 18.7.

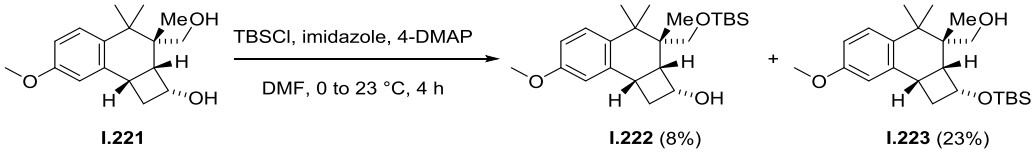
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3217 (*m*), 2970 (*m*), 2934 (*m*), 1606 (*m*), 1576 (*w*), 1495 (*m*), 1465 (*m*), 1365 (*w*), 1310 (*m*), 1247 (*s*), 1198 (*m*), 1112 (*m*), 1031 (*vs*), 849 (*m*), 808 (*m*), 735 (*s*), 703 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{24}O_3$ $[M]^+$: 276.1720; found: 276.1726.



The relative stereochemistry was assigned by NOE correlations.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-methoxy-3,4,4-trimethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalen-2-ol (I.222) and (2-((tert-butyldimethylsilyl)oxy)-7-methoxy-3,4,4-trimethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalen-3-yl)methanol (I.223):



To a solution of **I.221** (8.50 mg, 0.0308 mmol, 1 equiv) in dimethylformamide (0.15 mL) were added imidazole (4.19 mg, 0.0615 mmol, 2.00 equiv), *tert*-butyldimethylsilyl chloride (4.64 mg, 0.0308 mmol, 1 equiv) and 4-dimethylaminopyridine (0.376 mg, 0.00308 mmol, 0.100 equiv) subsequently. After 4 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (5 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **I.223** (2.8 mg, 23%) and **I.222** (1 mg, 8%) as a colorless oils.

Analytical data for I.223:

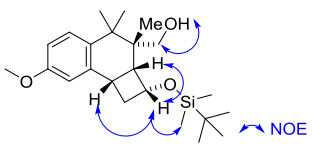
TLC (33% ethyl acetate in hexanes), R_f = 0.60 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (d, *J* = 8.6 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.64 (q, *J* = 8.6 Hz, 1H), 3.76 (s, 3H), 3.43 (d, *J* = 12.4 Hz, 1H), 3.22 (t, *J* = 12.0 Hz, 1H), 3.14 (q, *J* = 9.0 Hz, 1H), 3.00 (td, *J* = 8.8, 3.0 Hz, 1H), 2.87 (ddt, *J* = 12.4, 8.1, 4.0 Hz, 1H), 2.13 (q, *J* = 10.1 Hz, 1H), 1.32 (s, 3H), 1.14 (s, 3H), 1.00 (s, 3H), 0.92 (s, 9H), 0.14 (app d, *J* = 9.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.1, 140.3, 137.3, 124.9, 112.1, 110.9, 66.4, 64.1, 55.3, 50.4, 43.2, 40.8, 40.1, 27.9, 27.5, 25.8, 21.4, 18.8, 18.2, -4.9, -5.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3424 (*w*), 2956 (*m*), 1607 (*w*), 1576 (*w*), 1496 (*m*), 1472 (*m*), 1253 (*s*), 1198 (*m*), 1116 (*m*), 1077 (*m*), 1038 (*s*), 983 (*w*), 870 (*m*), 838 (*vs*), 782 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{23}H_{38}O_3Si$ $[M]^+$: 390.2585; found: 390.2597.



The relative stereochemistry and the position of the TBS protecting group were assigned by NOE correlations.

Analytical data for I.222:

Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.

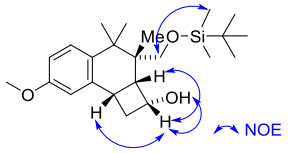
TLC (33% ethyl acetate in hexanes), R_f = 0.51 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (d, *J* = 8.5 Hz, 1H), 6.66 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 5.98 (d, *J* = 11.7 Hz, 1H), 4.52 – 4.33 (m, 1H), 3.78 (s, 3H), 3.53 – 3.39 (m, 2H), 3.09 (q, *J* = 8.7 Hz, 1H), 3.02 (td, *J* = 8.6, 3.5 Hz, 1H), 2.95 – 2.84 (m, 1H), 1.90 (q, *J* = 10.1 Hz, 1H), 1.31 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.1*, 140.7, 137.0, 124.9, 112.3, 111.2, 65.9, 65.5, 55.3, 49.9, 43.2, 41.8, 40.1, 28.3, 27.2, 25.9 (3C), 21.6, 19.0, 18.4, -5.4 (2C).

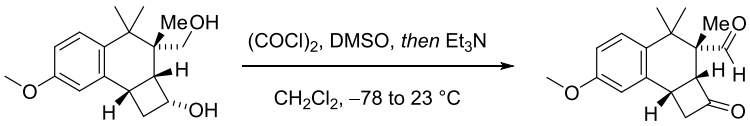
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3373 (*w*), 2930 (*m*), 2363 (*w*), 1653 (*w*), 1607 (*w*), 1559 (*w*), 1457 (*m*), 1252 (*m*), 1128 (*m*), 1038 (*s*), 839 (*vs*), 781 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{23}H_{38}O_3Si$ $[M]^+$: 390.2585; found: 390.2590.



The relative stereochemistry and the position of the TBS protecting group were assigned by NOE correlations.

7-Methoxy-3,4,4-trimethyl-2-oxo-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-3-carbaldehyde (I.218):



I.221 I.218

To a solution of oxalyl chloride (2 M in dichloromethane, 151 µL, 0.302 mmol, 2.20 equiv) in dichloromethane (1.5 mL) was added dimethyl sulfoxide (47.9 µL, 0.674 mmol, 4.90 equiv) at −78 °C. After stirring for 3 min, a solution of **I.221** (38.0 mg, 0.137 mmol, 1 equiv) dichloromethane (1 mL) was added and after further 25 min triethylamine (191 µL, 1.37 mmol, 10.0 equiv) was added. The reaction mixture was stirred for 10 min at −78 °C and was then directly warmed to 23 °C. After 10 min, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane

(3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes, triethylamine pretreated silica gel) to obtain **I.218** (35.5 mg, 95%) as a colorless oil.

Analytical data for I.218:

Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.

TLC (20% ethyl acetate in hexanes), R_f = 0.18 (ANIS).

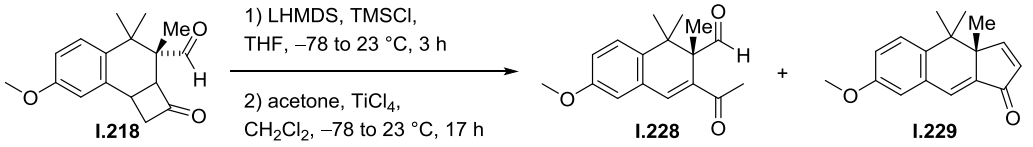
^{1}H NMR (400 MHz, C_6D_6) δ: 9.12 (br s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.68 – 6.59 (m, 2H), 3.31 (s, 3H), 3.24 (br s, 1H), 3.08 (ddd, *J* = 17.2, 9.6, 3.8 Hz, 1H), 2.95 (tdt, *J* = 9.6, 6.0, 1.1 Hz, 1H), 2.83 (ddd, *J* = 10.3, 3.7, 2.8 Hz, 1H), 1.05 (s, 3H), 1.01 (s, 3H), 0.73 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ: 206.7, 202.2, 159.2, 140.3, 135.5, 125.4, 113.4, 112.3, 63.9, 55.9, 54.7, 53.1, 39.7, 26.3, 25.9, 21.7*, 16.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2973 (*w*), 2933 (*w*), 2728 (*w*), 1774 (*vs*), 1718 (*s*), 1607 (*m*), 1574 (*w*), 1494 (*m*), 1465 (*m*), 1388 (*m*), 1298 (*m*), 1249 (*s*), 1155 (*m*), 1087 (*m*), 1034 (*s*), 854 (*w*), 820 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412; found: 272.1409.

3-Acetyl-6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalene-2-carbaldehyde (I.228) and 7-methoxy-3a,4,4-trimethyl-3a,4-dihydro-1H-cyclopenta[b]naphthalen-1-one (I.229):



To a solution of **I.218** (5.00 mg, 0.0184 mmol, 1 equiv) in tetrahydrofuran (0.2 mL) was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 22.0 μL, 0.0220 mmol, 1.20 equiv) at −78 °C. After 1 h, freshly distilled trimethylsilyl chloride (over CaH_2, 3.52 μL, 0.0275 mmol, 1.50 equiv) was added and the mixture was allowed to warm to 23 °C. After 3 h, dichloromethane (5 mL) was added, the reaction mixture was filtered through a small plug of Celite® and the filtrate was concentrated. The residue was used without further purification.

To acetone (2.03 μL, 0.0276 mmol, 1.50 equiv) in dichloromethane (0.1 mL) was added titanium(IV) chloride (3.04 μL, 0.0276 mmol, 1.50 equiv) followed by the addition of a solution of crude product in dichloromethane (0.3 mL) at −78 °C. The reaction mixture was allowed to warm to 23 °C over 17 h. pH7 Buffer solution (10 mL) and diethyl ether (10 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide trace amounts of **I.228** and **I.229** as colorless oils.

Analytical data for I.228:

TLC (20% ethyl acetate in hexanes), R_f = 0.14 (UV, CAM, $KMnO_4$).

^{1}H NMR (400 MHz, C_6D_6) δ: 9.90 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.89 (s, 1H), 6.69 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 3.33 (s, 3H), 1.90 (s, 3H), 1.26 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ: 200.4, 196.6, 158.6, 142.4, 138.5, 137.6, 131.3, 125.8, 116.7, 115.0, 54.9, 53.8, 40.7, 26.4, 25.0, 20.3, 14.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 2934 (*w*), 1775 (*m*), 1719 (*m*), 1652 (*m*), 1606 (*m*), 1570 (*m*), 1495 (*m*), 1464 (*m*), 1370 (*m*), 1259 (*s*), 1236 (*s*), 1195 (*m*), 1146 (*m*), 1091 (*m*), 1035 (*vs*), 928 (*m*), 905 (*m*), 816 (*m*), 736 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1407; found: 272.1407.

Analytical data for I.229:

TLC (20% ethyl acetate in hexanes), R_f = 0.26 (UV, CAM, $KMnO_4$).

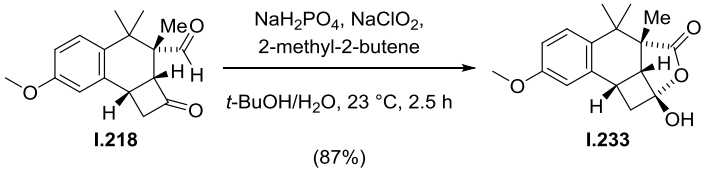
^{1}H NMR (400 MHz, C_6D_6) δ: 7.20 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 6.0, 1.1 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.24 (d, *J* = 6.0 Hz, 1H), 3.27 (s, 3H), 1.08 (s, 3H), 0.76 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ: 194.6, 162.4, 158.9, 143.1, 139.3, 136.4, 133.0, 126.1, 124.4, 115.9, 115.0, 54.9, 49.9, 39.6, 26.3, 20.4, 20.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (*w*), 2929 (*w*), 1689 (*vs*), 1645 (*vs*), 1605 (*m*), 1566 (*m*), 1482 (*w*), 1465 (*w*), 1372 (*w*), 1322 (*w*), 1249 (*m*), 1229 (*vs*), 1205 (*w*), 1146 (*w*), 1082 (*w*), 1057 (*w*), 1036 (*m*), 853 (*w*), 816 (*s*), 709 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{18}O_3$ $[M]^+$: 254.1301; found: 254.1301.

1a-Hydroxy-7-methoxy-3a,4,4-trimethyl-1,1a,1a1,3a,4,8b-hexahydro-3H-benzo[f]cyclobuta[cd]isobenzofuran-3-one (I.233):



A suspension of **I.218** (5.00 mg, 0.0184 mmol, 1 equiv) in *tert*-butanol (0.54 mL) and water (0.3 mL) was treated with 2-methyl-2-butene (2 M in tetrahydrofuran, 0.367 mL, 0.734 mmol, 40.0 equiv) at 0 °C. Sodium dihydrogen phosphate (22.0 mg, 0.184 mmol, 10.0 equiv) and sodium chlorite (16.6 mg, 0.184 mmol, 10.0 equiv) were added and the ice bath was removed. After 2.5 h, saturated aqueous sodium thiosulfate solution (10 mL), water (2 mL) and dichloromethane (5 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **I.233** (4.6 mg, 87%) as a white amorphous solid.

Analytical data for I.233:

TLC (50% ethyl acetate in hexanes), R_f = 0.42 (CAM, ANIS, $KMnO_4$).

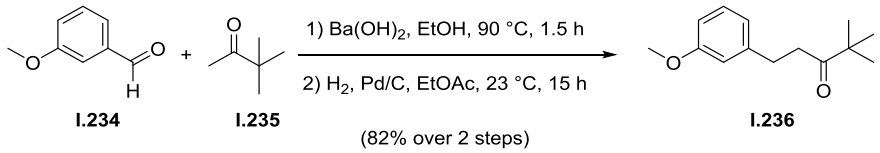
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, *J* = 8.7 Hz, 1H), 6.72 (ddd, *J* = 8.7, 2.8, 0.9 Hz, 1H), 6.60 (dd, *J* = 2.8, 1.1 Hz, 1H), 3.76 (s, 3H), 3.48 (td, *J* = 10.1, 2.7 Hz, 2H), 3.15 (dt, *J* = 9.5, 0.8 Hz, 1H), 3.02 (dd, *J* = 12.5, 10.2 Hz, 1H), 2.56 (ddd, *J* = 12.5, 2.8, 1.1 Hz, 1H), 1.63 (s, 3H), 1.42 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.5, 158.5, 137.9, 136.7, 125.6, 113.7, 112.2, 102.6, 55.3, 51.3, 50.7, 43.3, 38.4, 27.8, 25.7, 20.4, 19.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3362 (*m*), 2971 (*m*), 1768 (*s*), 1743 (*s*), 1608 (*m*), 1574 (*w*), 1499 (*m*), 1466 (m), 1366 (*w*), 1318 (*w*), 1298 (*m*), 1286 (*m*), 1253 (*vs*), 1222 (*s*), 1161 (*s*), 1101 (*w*), 1074 (*m*), 1036 (*m*), 1018 (*s*), 950 (*w*), 908 (*m*), 875 (*w*), 784 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{20}O_4$ $[M]^+$: 288.1356; found: 288.1360.

1-(3-Methoxyphenyl)-4,4-dimethylpentan-3-one (I.236):



I.234 I.235 I.236

A mixture of *m*-anisaldehyde (**I.234**) (8.95 mL, 73.4 mmol, 1 equiv), pinacolone (**I.235**) (13.8 mL, 110 mmol, 1.50 equiv) and barium hydroxide (1.89 g, 11.0 mmol, 0.150 equiv) in ethanol (37 mL) was heated to 90 °C. After 2 h, the reaction mixture was concentrated, the residue was dissolved in ethyl acetate (460 mL) and filtered through a short pad of Celite®. To this solution was added Pd/C (10% Pd on activated charcoal, 0.781 g, 0.734 mmol, 0.0100 mmol) and the resulting suspension was sparged with hydrogen gas for 20 min. Stirring under hydrogen atmosphere was continued for 15 h, then Celite® was added and the mixture was filtered through a pad of Celite®. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **I.236** (13.3 g, 82% over 2 steps) as a colorless oil.

Analytical data for I.236:

TLC (20% ethyl acetate in hexanes), R_f = 0.54 (ANIS).

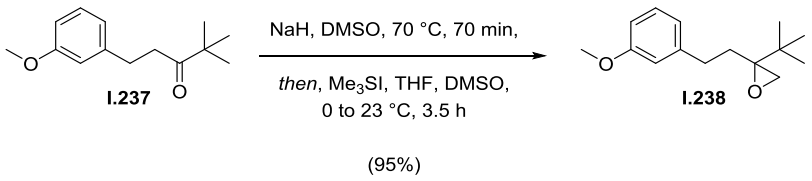
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 – 7.16 (m, 1H), 6.78 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.76 – 6.72 (m, 2H), 3.79 (s, 3H), 2.88 – 2.76 (m, 4H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 215.0, 159.7, 143.3, 129.5, 120.8, 114.2, 111.4, 55.2, 44.2, 38.5, 30.2, 26.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3315 (*m*), 3297 (*m*), 3256 (*m*), 3183 (*m*), 3106 (*m*), 2957 (*m*), 2835 (*m*), 2707 (*m*), 2617 (*m*), 2125 (*w*), 1703 (*w*), 1651 (*m*), 1584 (*s*), 1517 (*s*), 1476 (*vs*), 1394 (*s*), 1364 (*s*), 1317 (*w*), 1226 (*s*), 1151 (*vs*), 1125 (*s*), 1099 (*s*), 1025 (*s*), 978 (*s*), 928 (*s*), 787 (s), 762 (*s*), 723 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1458; found: 220.1459.

2-(*tert*-Butyl)-2-(3-methoxyphenethyl)oxirane (I.238):



A suspension of sodium hydride (60% dispersion in mineral oil, 3.92 g, 98.0 mmol, 2.00 equiv) in dimethyl sulfoxide (49 mL) was heated to 70 °C until gas evolution ceased. After 70 min, the reaction mixture was cooled to 23 °C, diluted with tetrahydrofuran (49 mL) and cooled to 0 °C. A solution of trimethylsulfonium iodide (12.0 g, 58.8 mmol, 1.20 equiv) in dimethyl sulfoxide (45 mL) was added and after stirring for 20 min, **I.237** (10.8 g, 49.0 mmol, 1 equiv) was added slowly. The mixture was allowed to warm to 23 °C over 3 h, cooled back to 0 °C and diluted with water (200 mL).The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **I.238** (10.9 g, 95%) as a colorless oil.

Analytical data for I.238:

TLC (20% ethyl acetate in hexanes), R_f = 0.54 (CAM, ANIS).

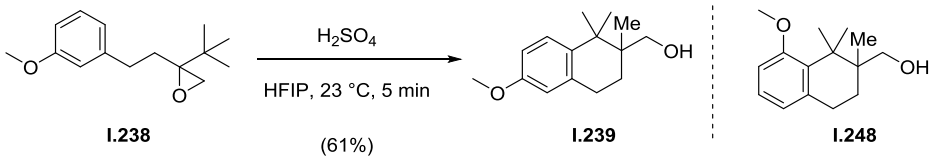
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 – 7.17 (m, 1H), 6.80 – 6.76 (m, 1H), 6.76 – 6.70 (m, 2H), 3.80 (s, 3H), 2.78 (dd, *J* = 4.2, 0.8 Hz, 1H), 2.67 (d, *J* = 4.2 Hz, 1H), 2.54 (ddd, *J* = 13.5, 11.5, 5.1 Hz, 1H), 2.44 (ddd, *J* = 13.5, 11.6, 5.8 Hz, 1H), 2.13 (ddd, *J* = 14.6, 11.6, 5.8 Hz, 1H), 2.02 (ddd, *J* = 14.6, 11.7, 5.1 Hz, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.8, 144.0, 129.5, 120.8, 114.3, 111.2, 63.5, 55.3, 48.1, 34.1, 31.4, 30.8, 26.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (*m*), 2872 (*w*), 2835 (*w*), 1602 (*s*), 1585 (*s*), 1490 (*s*), 1465 (*s*), 1455 (*s*), 1436 (*m*), 1394 (*w*), 1364 (*w*), 1284 (*w*), 1261 (*vs*), 1166 (*s*), 1153 (*vs*), 1055 (*s*), 1039 (*vs*), 910 (*m*), 836 (*m*), 777 (*vs*), 745 (*m*), 696 (*vs*) cm^{-1}.

HRMS (ESI) calcd for $C_{15}H_{22}O_2$ $[M]^+$: 234.1614; found: 234.1621.

(6-Methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (I.239):



I.238 I.239 I.248

To a solution of **I.238** (234 mg, 1.00 mmol, 1 equiv) in hexafluoro-2-propanol (10 mL) was added sulfuric acid (40 µL). After 5 min, the reaction mixture was cooled to 0 °C and saturated aqueous sodium bicarbonate solution (10 mL), saturated aqueous sodium chloride solution (10 mL) and diethyl ether (20 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (11% ethyl acetate in hexanes) to afford **I.239** (143 mg, 61%) as a yellow oil.

Note: During the screening for the optimal reaction conditions, the o-product **I.248** *was isolated and analyzed.*

Analytical data for I.239:

TLC (20% ethyl acetate in hexanes), R_f = 0.13 (CAM, ANIS).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, *J* = 8.9 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 3.60 – 3.49 (m, 2H), 2.88 – 2.68 (m, 2H), 1.87 – 1.65 (m, 2H), 1.21 (app d, *J* = 10.9 Hz, 6H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.0, 138.3, 136.7, 128.0, 112.9, 112.6, 67.3, 55.2, 39.2, 38.7, 27.9, 27.2, 26.6, 25.4, 19.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3358 (*m*), 2973 (*m*), 2956 (*m*), 2929 (*m*), 1609 (*s*), 1500 (*s*) 1459 (*s*), 1448 (*s*), 1432 (*m*), 1361 (*m*), 1317 (*s*), 1246 (*s*), 1232 (*s*), 1198 (*m*), 1164 (*m*), 1084 (*m*), 1047 (*s*), 1033 (*vs*), 1022 (*vs*), 993 (*s*), 948 (*m*), 889 (*m*), 848 (*s*), 823 (*vs*), 754 (*m*), 714 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{15}H_{22}O_2$ $[M]^+$: 234.1614; found: 234.1617.

Analytical data for I.248:

TLC (20% ethyl acetate in hexanes), R_f = 0.29 (CAM).

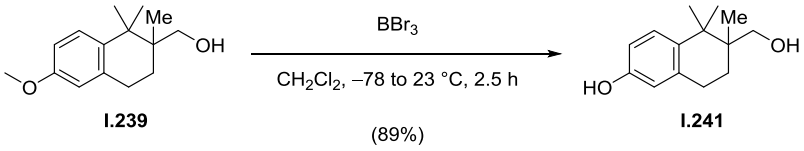
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (t, *J* = 7.8 Hz, 1H), 6.74 – 6.68 (m, 2H), 3.80 (s, 3H), 3.59 (s, 2H), 2.92 – 2.70 (m, 3H), 1.80 – 1.61 (m, 2H), 1.33 (app d, *J* = 9.0 Hz, 6H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.5, 138.1, 133.9, 126.1, 122.1, 109.5, 66.9, 55.2, 40.5, 39.3, 27.2, 26.9, 23.5, 21.9, 18.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3384 (*w*), 2969 (*m*), 2938 (*m*), 1576 (*m*), 1452 (*s*), 1436 (*s*), 1362 (*m*), 1248 (*vs*), 1191 (*m*), 1109 (*m*), 1074 (*s*), 1058 (*s*), 1022 (*vs*), 1005 (*s*), 953 (*m*), 880 (m), 811 (*m*), 779 (*s*), 754 (*s*), 740 (*vs*).

HRMS (ESI) calcd for $C_{15}H_{22}O_2$ $[M]^+$: 234.1614; found: 234.1616.

6-(Hydroxymethyl)-5,5,6-trimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (I.241):



I.239 I.241

To a solution **I.239** (234 mg, 1 mmol, 1 equiv) in dichloromethane (5 mL) at −78 °C was added dropwise a solution of boron tribromide (1 M in dichloromethane, 5.00 mL, 5.00 mmol, 5.00 equiv). The reaction mixture was allowed to warm to 23 °C over 2.5 h, cooled back to 0 °C and excess boron tribromide was carefully quenched by addition of methanol (1 mL). Water (40 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to provide **I.241** (197 mg, 89%) as an orange solid.

Analytical data for I.241:

TLC (50% ethyl acetate in hexanes), R_f = 0.38 (CAM).

^{1}H NMR (400 MHz, Acetone-d_6) δ: 7.93 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 6.61 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 3.58 (t, *J* = 5.1 Hz, 1H), 3.49 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.43 (dd, *J* = 10.5, 5.4 Hz, 1H), 2.76 (ddd, *J* = 17.4, 8.8, 6.3 Hz, 1H), 2.62 (dt, *J* = 17.4, 6.1 Hz, 1H),

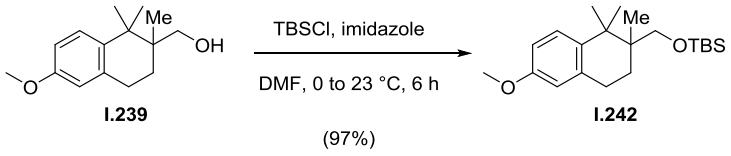
1.81 (dt, *J* = 13.4, 6.2 Hz, 1H), 1.63 (ddd, *J* = 13.3, 8.7, 6.3 Hz, 1H), 1.19 (s, 3H), 1.16 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, Acetone-d_6) δ: 155.3, 137.9, 137.3, 128.5, 115.2, 114.3, 66.5, 39.8, 39.1, 28.3, 27.8, 26.9, 25.5, 19.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3379 (*m*), 3166 (*m*), 2970 (*m*), 2931 (*m*), 1616 (*m*), 1585 (*m*), 1499 (*m*), 1456 (*m*), 1432 (*m*), 1352 (*m*), 1293 (*m*), 1258 (*s*), 1232 (*s*), 1159 (*m*), 1137 (*m*), 1091 (*m*), 1020 (*vs*), 940 (*m*), 931 (*m*), 896 (*m*), 867 (*m*), 807 (*vs*), 738 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1458; found: 220.1457

***tert*-Butyl((6-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methoxy) dimethylsilane (I.242):**



To a solution of **I.239** (100 mg, 0.427 mmol, 1 equiv) in dimethylformamide (1.3 mL) were added imidazole (58.1 mg, 0.853 mmol, 2.00 equiv) and *tert*-butyldimethylsilyl chloride (96.5 mg, 0.640 mmol, 1.50 equiv) at 0 °C. After 6 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **I.242** (144 mg, 97%) as a colorless oil.

Analytical data for I.242:

TLC (20% ethyl acetate in hexanes), R_f = 0.66 (CAM).

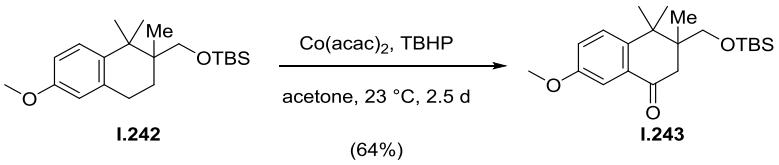
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.5 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 3.79 (s, 3H), 3.44 (d, *J* = 1.9 Hz, 2H), 2.86 – 2.65 (m, 2H), 1.82 (dt, *J* = 12.7, 6.1 Hz, 1H), 1.67 – 1.54 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H), 0.95 (s, 3H), 0.91 (s, 9H), 0.03 (app d, *J* = 6.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.9, 138.8, 137.2, 128.0, 112.9, 112.4, 67.0, 55.2, 39.4, 38.6, 28.3, 27.4, 26.7, 26.0, 25.3, 19.4, 18.3, -5.4, -5.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*m*), 2928 (*m*), 2856 (*m*), 1718 (*w*), 1610 (*w*), 1499 (*m*), 1463 (*m*), 1362 (w), 1318 (*w*), 1251 (*s*), 1235 (*m*), 1203 (*w*), 1117 (*m*), 1075 (*s*), 1040 (*s*), 1006 (*m*), 835 (*vs*), 810 (*s*), 773 (*vs*), 666 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{21}H_{36}O_2Si$ $[M]^+$: 348.2479; found: 348.2496.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-methoxy-3,4,4-trimethyl-3,4-dihydro-naphthalen-1(2H)-one (I.243):



I.242 I.243

To a solution of **I.242** (1.29 g, 3.70 mmol, 1 equiv) in acetone (7 mL) was added cobalt(II) acetylacetonate (190 mg, 0.74 mmol, 0.200 equiv). To the resulting purple suspension was added dropwise *tert*-butyl hydroperoxide (5.5 M in decane, 2.69 mL, 14.8 mmol, 4.00 equiv). After 2.5 d, saturated aqueous sodium chloride solution (15 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **I.243** (855 mg, 64%) as a yellow oil.

Analytical data for I.243:

Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.

TLC (20% ethyl acetate in hexanes), R_f = 0.53 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 3.0 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.08 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.83 (s, 3H), 3.53 (d, *J* = 10.0 Hz, 1H), 3.45 (d, *J* = 9.9 Hz, 1H), 2.78 (d, *J* =

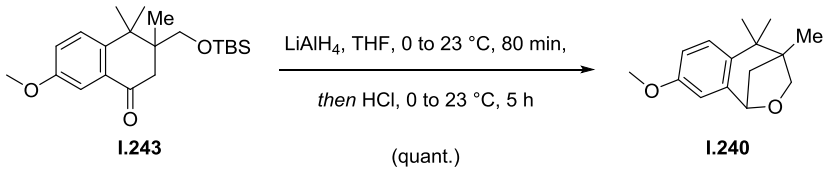
17.4 Hz, 1H), 2.53 (d, *J* = 17.4 Hz, 1H), 1.33 (app d, *J* = 4.6 Hz, 6H), 0.98 (s, 3H), 0.81 (s, 9H), -0.06 (d, *J* = 9.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.0, 157.7, 145.3, 132.6, 127.3, 122.1, 108.5, 67.9, 55.6, 45.0, 43.1, 39.3, 26.9*, 25.9, 24.8*, 19.8, 18.3, -5.6, -5.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (*m*), 2929 (*m*), 2856 (*m*), 1684 (*m*), 1608 (*m*), 1493 (*m*), 1464 (*m*), 1416 (*m*), 1322 (*m*), 1282 (*m*), 1249 (*m*), 1181 (*w*), 1114 (*m*), 1078 (*m*), 1034 (*m*), 1006 (*w*), 836 (*vs*), 775 (*s*), 669 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{21}H_{35}O_3Si$ $[M+H]^+$: 363.2350; found: 363.2351.

8-Methoxy-4,5,5-trimethyl-1,3,4,5-tetrahydro-1,4-methanobenzo[c]oxepine (I.240):



To a solution of **I.243** (100 mg, 0.276 mmol, 1 equiv) in tetrahydrofuran (9.2 mL) was added lithium aluminum hydride (126 mg, 3.31 mmol, 12.0 equiv) at 0 °C. The reaction was allowed to warm to 23 °C and after 80 min, the mixture was cooled back to 0 °C. An aqueous hydrochloric acid solution (2 M, 3 mL) was added very carefully followed by addition of concentrated aqueous hydrochloric acid solution (37%, 3 mL). The reaction mixture was allowed to warm to 23 °C and after 5 h, ethyl acetate (10 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to yield **I.240** (64 mg, quant.) as a colorless solid.

Analytical data for I.240:

TLC (33% ethyl acetate in hexanes), R_f = 0.45 (CAM).

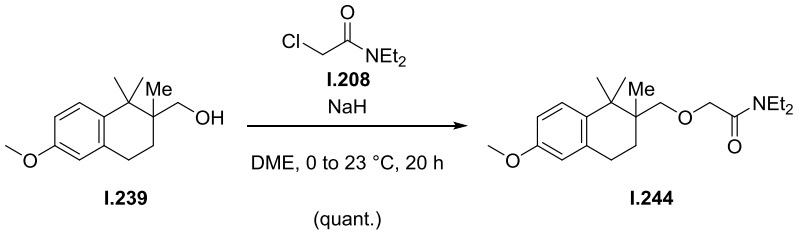
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.5 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 4.73 (d, *J* = 5.0 Hz, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 3.78 (s, 3H), 3.50 (d, *J* = 8.6 Hz, 1H), 2.26 (d, *J* = 11.3 Hz, 1H), 1.85 (dd, *J* = 11.5, 5.0 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.6, 139.5, 136.9, 128.5, 114.5, 111.3, 79.0, 75.1, 55.3, 46.8, 41.8, 39.9, 29.4, 24.1, 19.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2963 (*m*), 2937 (*m*), 2877 (*m*), 1607 (*m*), 1578 (*w*), 1504 (*m*), 1452 (*m*), 1392 (*w*), 1334 (*w*), 1314 (*m*), 1265 (*m*), 1240 (*vs*), 1171 (*m*), 1154 (*m*), 1119 (*w*), 1074 (*w*), 1035 (*vs*), 1026 (*vs*), 991 (*w*), 964 (*w*), 907 (*m*), 856 (*s*), 822 (*m*), 807 (*m*), 680 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{20}O_2$ $[M]^+$: 232.1458; found: 232.1462.

N,N-Diethyl-2-((6-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methoxy) acetamide (I.244):



To a solution of **I.239** (125 mg, 0.533 mmol, 1 equiv) in 1,2-dimethoxyethane (2.7 mL) was added sodium hydride (60% dispersion in mineral oil, 53.3 mg, 1.60 mmol, 3.00 equiv) at 0 °C and after 20 min 2-chloro-*N*,*N*-diethylacetamide (**I.208**) (110 μL, 0.800 mmol, 1.50 equiv). The reaction was allowed to warm slowly to 23 °C over 20 h and was diluted with saturated aqueous ammonium chloride solution (10 mL) and water (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20 to 33% ethyl acetate in hexanes) to afford **I.244** (185 mg, quant.) as a yellow oil.

Analytical data for I.244:

TLC (50% ethyl acetate in hexanes), R_f = 0.38 (ANIS, CAM).

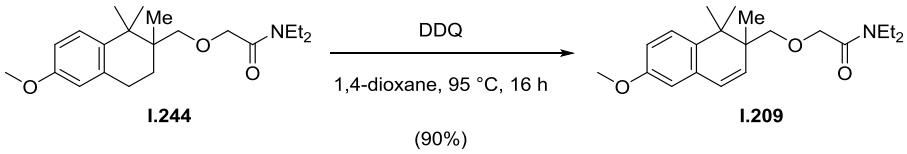
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 4.09 (d, *J* = 0.8 Hz, 2H), 3.76 (s, 3H), 3.43 – 3.29 (m, 6H), 2.81 (ddd, *J* = 17.6, 8.6, 6.4 Hz, 1H), 2.71 (dt, *J* = 17.4, 6.1 Hz, 1H), 1.85 (dt, *J* = 13.4, 6.1 Hz, 1H), 1.69 (ddd, *J* = 13.4, 8.7, 6.3 Hz, 1H), 1.23 – 1.15 (m, 9H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.5, 157.0, 138.3, 136.7, 127.9, 112.9, 112.5, 76.3, 71.3, 55.2, 41.0, 39.8, 38.9, 38.7, 27.9, 27.6, 26.5, 25.3, 19.7, 14.4, 12.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2969 (*m*), 2935 (*m*), 1643 (*vs*), 1608 (*m*), 1576 (*w*), 1499 (*s*), 1461 (*s*), 1434 (*m*), 1381 (*m*), 1364 (*m*), 1316 (*m*), 1289 (*m*), 1263 (*s*), 1234 (*s*), 1204 (*m*), 1164 (*m*), 1089 (*vs*), 1036 (*vs*), 968 (*w*), 892 (*w*), 846 (*m*), 801 (*m*), 733 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{21}H_{33}O_3N$ $[M]^+$: 347.2455; found: 347.2460.

N,N-Diethyl-2-((6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy) acetamide (I.209):



I.244 **I.209**

To **I.244** (2.00 g, 5.76 mmol, 1 equiv) in 1,4-dioxane (58 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (7.84 g, 34.5 mmol, 6.00 equiv) and the reaction mixture was heated to 95 °C. After 16 h, saturated aqueous sodium bicarbonate solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 200 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **I.209** (1.78 g, 90%) as an orange oil.

For the analytical data see the experimental procedure *vide infra*.

10.2.2 CADA Reaction

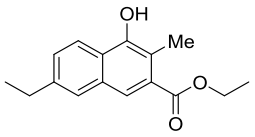
10.2.2.1 Synthesis of Precursors

For the synthesis of **I.68**, **I.77**, **I.78**, **I.81** and **I.91** see the experimental part of salimabromide.

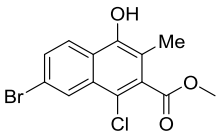
For the synthesis of **II.101**, **II.103** see J. M. Hammann, T. A. Unzner, T. Magauer, *Chem. Eur. J.* **2014**, *20*, 6733–6738.

For the synthesis of **II.102** see T. A. Unzner, A. Grossmann, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9763–9767.

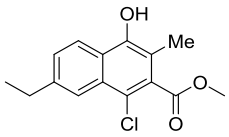
For the synthesis of **II.104** see A. J. Brockway, M. González-López, J. C. Fettinger, J. T. Shaw, *J. Org. Chem.* **2011**, *76*, 3515–3518.



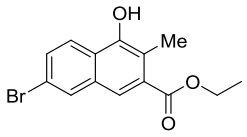
I.68



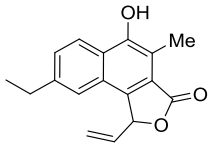
I.77



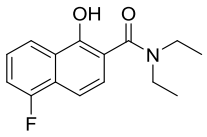
I.78



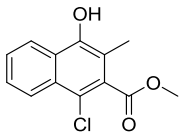
I.81



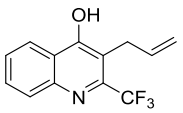
I.91



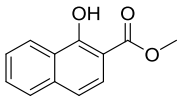
II.101



II.102

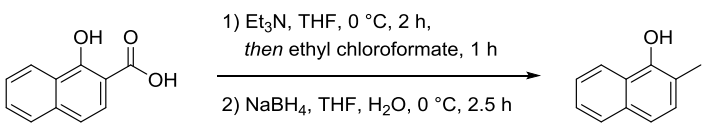


II.103



II.104

2-Methylnaphthalen-1-ol (I.34):



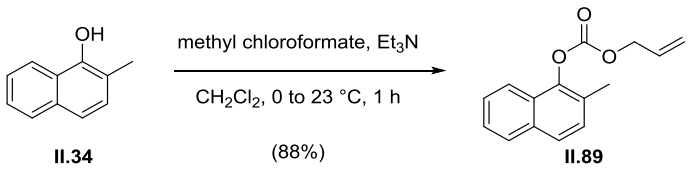
II.105 (86% over 2 steps) **II.34**

To a solution of 1-hydroxy-2-naphthoic acid (**II.105**) (4.5 g, 24 mmol, 1 equiv) in tetrahydrofuran (150 mL) was added triethylamine (8.7 mL, 62 mmol, 2.6 equiv). The reaction mixture was cooled to 0 °C and stirred for 2 h. Ethyl chloroformate (6.0 mL, 62 mmol, 2.6 equiv) was added dropwise. After 1 h, the suspension was filtered and the residue was

washed with tetrahydrofuran (10 mL). The filtrate was concentrated and redissolved in tetrahydrofuran (45 mL). The resulting solution was added to a stirred mixture of sodium borohydride (7.3 g, 0.19 mol, 8.0 equiv) in water (45 mL) at 0 °C. The resulting yellow mixture was allowed to stir for 2.5 h before aqueous hydrogen chloride solution (2 M; 10 mL) was added carefully until gas evolution ceased. The mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% diethyl ether in hexanes) to afford **II.34** (3.5 g, 86% over 2 steps) as colorless crystals.

The obtained analytical data were in full agreement with those reported in the literature.[202]

Allyl (2-methylnaphthalen-1-yl) carbonate (I.89):



To a solution of 2-methylnaphthalen-1-ol (**II.34**) (1.90 mmol, 300 mg, 1 equiv) and methyl chloroformate (22.0 μL, 2.10 mmol, 1.10 equiv) in dichloromethane was added triethylamine (30.0 μL, 2.10 mmol, 1.10 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C and was stirred for 1 h. The resulting mixture was treated with water (25 mL) and was partitioned between water (20 mL) and dichloromethane (20 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% diethyl ether in hexanes) to afford **II.89** (405 mg, 88%) as a colorless oil.

Analytical data for II.89:

TLC (20% diethyl ether in hexanes), R_f = 0.45 (ANIS, UV).

^{1}H NMR (599 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.4, 1.0 Hz, 1H), 7.83 (d, *J* = 8.2, 0.9 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (td, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.46 (td, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.35 (d,

J = 8.5 Hz, 1H), 6.05 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.47 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.36 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.80 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 153.3, 144.5, 133.3, 131.4, 128.9, 128.0, 127.2, 126.9, 126.7, 126.3, 125.8, 120.7, 119.6, 69.5, 16.3.

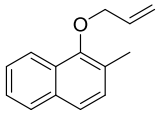
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3052 (*w*), 3018 (*w*), 2865 (*w*), 1759 (*s*), 1603 (*w*), 1608 (*w*), 1360 (*w*), 1267 (*m*), 1225 (*vs*), 1178 (*s*), 1339 (*m*), 1090 (*w*), 944 (*m*), 810 (*m*), 781 (*w*), 743 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{14}O_3$ $[M]^+$: 242.0937; found: 242.0940.

10.2.2.2 Synthesis of Allyl Naphthol Ether

General Procedure for the Allylation of Naphthols:

To a solution of naphthol (1 equiv) in dimethylformamide (0.3 m) were subsequently added potassium carbonate (1.50 equiv) and allyl bromide (1.10 equiv) and the suspension was heated to 65 °C. After 1.5–2 h, saturated aqueous ammonium chloride solution was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 ×). The combined organic layers were washed with aqueous hydrochloric acid solution (2 M) and saturated aqueous sodium chloride solution. The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel.



II.91

Following the general procedure except for heating the reaction for 17.5 h, naphthol **II.34** (3.0 g, 19 mmol) provided the allyl ether **II.91** (2.0 g, 53%) as a light yellow oil after flash column chromatography on silica gel (2% ethyl acetate in hexanes).

Analytical data for II.91:

TLC (20% diethyl ether in hexanes), R_f = 0.40 (ANIS, UV).

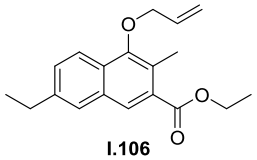
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.05 (ddt, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.59 (d, *J* = 9.8 Hz, 1H), 6.10 (d, *J* = 9.7 Hz, 1H), 5.58 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.01 (ddt, *J* = 17.0, 2.0, 1.4 Hz, 1H),

4.93 (ddt, *J* = 10.1, 1.9, 0.9 Hz, 1H), 2.67 (ddt, *J* = 13.6, 7.4, 1.1 Hz, 1H), 2.29 (ddt, *J* = 13.6, 7.2, 1.3 Hz, 1H), 1.27 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 203.1, 139.6, 138.5, 134.5, 133.5, 129.4, 128.0, 127.4, 127.1, 124.0, 118.2, 49.3, 44.6, 24.8.

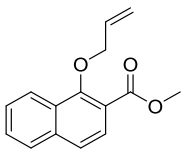
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928 (*w*), 1673 (*vs*), 1642 (*m*), 1598 (*s*), 1449 (*w*), 13.20 (*m*), 1268 (*m*), 1233 (*m*), 985 (*m*), 919 (*m*), 792 (*vs*), 693.2 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{14}O$ $[M]^+$: 198.1039; found: 198.1043.



I.106

Following the general procedure, naphthol **I.68** (300 mg, 1.16 mmol) provided the allyl ether **I.106** (274 mg, 79%) as a light yellow oil after flash column chromatography on silica gel (2% ethyl acetate in hexanes). For the analytical data see the experimental procedure for salimabromide.



II.105

Following the general procedure, naphthol **II.104** (100 mg, 0.495 mmol) provided the allyl ether **II.105** (108 mg, 90%) as a colorless oil after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

Analytical data for II.105:

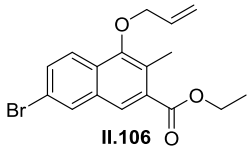
TLC (20% ethyl acetate in hexanes), R_f = 0.58 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 – 8.26 (m, 1H), 7.89 – 7.82 (m, 2H), 7.62 (dt, *J* = 8.7, 0.6 Hz, 1H), 7.61 – 7.51 (m, 2H), 6.23 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.49 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.33 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.67 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.9, 157.1, 136.9, 133.9, 129.0, 128.5, 128.0, 126.8, 126.7, 123.9, 123.9, 119.7, 118.1, 77.0, 52.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3070 (*w*), 2950 (*w*), 1723 (*vs*), 1626 (*w*), 1598 (*w*), 1570 (*w*), 1504 (*w*), 1464 (*w*), 1435 (*m*), 1393 (*w*), 1342 (*s*), 1278 (*s*), 1237 (*s*), 1204 (*m*), 1152 (*m*), 1132 (*s*), 1081 (*s*), 980 (*m*), 929 (*w*), 828 (*w*), 768 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{14}O_3$ $[M]^+$: 242.0937; found: 242.0939.



Following the general procedure, naphthol **I.81** (100 mg, 0.323 mmol) provided the allyl ether **II.106** (89 mg, 79%) as a light yellow solid after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

Analytical data for II.106:

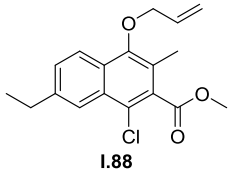
TLC (20% ethyl acetate in hexanes), R_f = 0.64 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.62 (dd, *J* = 9.0, 1.9 Hz, 1H), 6.18 (ddt, *J* = 17.9, 10.6, 5.5 Hz, 1H), 5.51 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.33 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.61 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H).

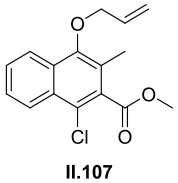
^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.6, 153.6, 133.5, 133.2, 131.4, 131.4, 130.9, 128.5, 127.3, 126.2, 124.2, 120.3, 118.0, 75.0, 61.4, 14.5, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (*w*), 2930 (*w*), 1719 (*vs*), 1583 (*w*), 1564 (*w*), 1446 (*w*), 1382 (*w*), 1346 (*m*), 1317 (*m*), 1273 (*vs*), 1235 (*m*), 1209 (*m*), 1192 (*m*), 1165 (*w*), 1108 (*m*), 1048 (*s*), 1011 (*w*), 993 (*w*), 905 (*m*), 824 (*m*), 778 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{17}O_3{}^{79}Br$ $[M]^+$: 348.0356; found: 348.0355.



Following the general procedure, naphthol **I.78** (100 mg, 0.359 mmol) provided the allyl ether **I.88** (103 mg, 90%) as a colorless oil after flash column chromatography on silica gel (5% ethyl acetate in hexanes). For the analytical data see the experimental procedure for salimabromide.



Following the general procedure, naphthol **II.102** (180 mg, 0.718 mmol) provided the allyl ether **II.107** (185 mg, 89%) as a yellow oil without further purification.

Analytical data for II.107:

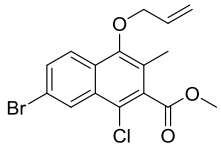
TLC (9% ethyl acetate in hexanes), R_f = 0.32 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (dd, *J* = 6.1, 3.5 Hz, 1H), 8.10 (dd, *J* = 6.2, 3.5 Hz, 1H), 7.59 (dd, *J* = 6.4, 3.2 Hz, 2H), 6.18 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.51 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.46 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.02 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.0, 152.0, 133.4, 133.3, 130.2, 129.4, 127.8, 127.3, 125.2, 124.0, 123.9, 122.5, 118.1, 75.1, 52.9, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 1735 (*vs*), 1592 (*w*), 1436 (*m*), 1385 (*m*), 1331 (*s*), 1280 (*vs*), 1239 (*s*), 1213 (*s*), 1171 (*m*), 1103 (*m*), 1051 (*s*), 972 (*m*), 924 (*s*), 863 (*w*), 764 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{15}O_3{}^{35}Cl$ $[M]^+$: 290.0704; found: 290.0707.



II.108

Following the general procedure, naphthol **I.77** (200 mg, 0.607 mmol) provided the allyl ether **II.108** (208 mg, 93%) as a light yellow oil after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

Analytical data for II.108:

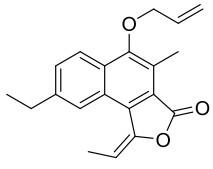
TLC (20% ethyl acetate in hexanes), R_f = 0.55 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 1.9 Hz, 1H), 7.94 (d, *J* = 8.9 Hz, 1H), 7.63 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.14 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.48 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.33 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.43 (dt, *J* = 5.5, 1.4 Hz, 2H), 4.01 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 152.1, 134.4, 133.1, 131.2, 131.2, 128.0, 127.4, 124.6, 124.4, 122.7, 122.0, 118.3, 75.3, 52.9, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (*w*), 1735 (*vs*), 1584 (*m*), 1436 (*m*), 1405 (*w*), 1384 (*w*), 1346 (*w*), 1315 (*s*), 1267 (*s*), 1230 (*s*), 1205 (*m*), 1169 (*m*), 1111 (*m*), 1075 (*m*), 1051 (*s*), 958 (*m*), 931 (*s*), 872 (*w*), 824 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{14}O_3{}^{79}Br^{35}Cl$ $[M]^+$: 367.9809; found: 367.9808.



II.109

Following the general procedure, naphthol **I.91** (50 mg, 0.186 mmol) provided the allyl ether **II.109** (32 mg, 55%) as a white solid after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

Analytical data for II.109:

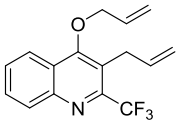
TLC (20% ethyl acetate in hexanes), R_f = 0.61 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 8.7 Hz, 1H), 8.03 (d, *J* = 1.5 Hz, 1H), 7.55 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.20 (ddd, *J* = 17.3, 10.7, 5.4 Hz, 1H), 6.15 (q, *J* = 7.2 Hz, 1H), 5.51 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.34 (dt, *J* = 10.5, 1.7 Hz, 1H), 4.49 (dd, *J* = 5.7, 1.4 Hz, 2H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.72 (s, 3H), 2.15 (d, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.7, 154.4, 147.1, 144.1, 133.4, 132.7, 130.4, 129.9, 126.7, 124.0, 123.7, 123.2, 122.7, 118.2, 108.5, 75.2, 29.4, 15.7, 12.5, 11.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2983 (*w*), 2925 (*w*), 1738 (*s*), 1464 (*w*), 1447 (*w*), 1373 (*m*), 1300 (*w*), 1236 (*vs*), 1114 (*w*), 1097 (*w*), 1045 (*s*), 1013 (*w*), 918 (*w*), 846 (*w*), 734 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.1407; found: 308.1408.



II.110

Following the general procedure, naphthol **II.103** (60 mg, 0.237 mmol) provided the allyl ether **II.110** (56 mg, 80%) as a light pink oil after flash column chromatography on silica gel (5% ethyl acetate in hexanes).

Analytical data for II.110:

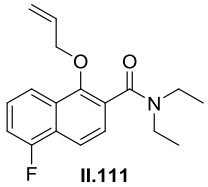
TLC (20% ethyl acetate in hexanes), R_f = 0.58 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 6.19 (ddt, *J* = 16.1, 10.6, 5.4 Hz, 1H), 6.01 (ddt, *J* = 16.4, 10.2, 5.9 Hz, 1H), 5.55 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 5.05 (dd, *J* = 19.5, 13.7 Hz, 2H), 4.65 (d, *J* = 5.2 Hz, 2H), 3.74 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.1, 147.9 (q, *J* = 32.5 Hz) 147.3, 135.9, 132.7, 130.6, 130.3, 128.5, 124.7, 122.9, 122.1, 122.1 (q, *J* = 276.7 Hz), 118.4, 116.4, 76.2, 29.8 (t, *J* = 2.6 Hz).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3083 (*w*), 2984 (*w*), 2874 (*w*), 1640 (*w*), 1566 (*w*), 1493 (*w*), 1382 (*m*), 1353 (*m*), 1342 (*s*), 4283 (*m*), 1250 (*w*), 1182 (*s*), 1122 (*vs*), 1107 (*vs*), 1002 (*s*), 964 (*m*), 919 (*m*), 768 (*vs*), 726 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{15}ONF_3$ $[M+H]^+$: 294.1100; found: 294.1109.



II.111

Following the general procedure, naphthol **II.101** (60 mg, 0.230 mmol) provided the allyl ether **II.111** (75 mg, quant.) as a yellow oil after flash column chromatography on silica gel (20% ethyl acetate in hexanes).

Analytical data for II.111:

TLC (20% ethyl acetate in hexanes), R_f = 0.17 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.89 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.44 (ddd, *J* = 8.5, 7.7, 5.4 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.18 (ddd, *J* = 10.5, 7.7, 1.0 Hz, 1H), 6.11 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.45 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.26 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.64 (dd, *J* = 33.0, 5.5 Hz, 2H), 3.85 (q, *J* = 7.2 Hz, 1H), 3.38 (dd, *J* = 13.6, 6.9 Hz, 1H), 3.21 (dq, *J* = 24.8, 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H).

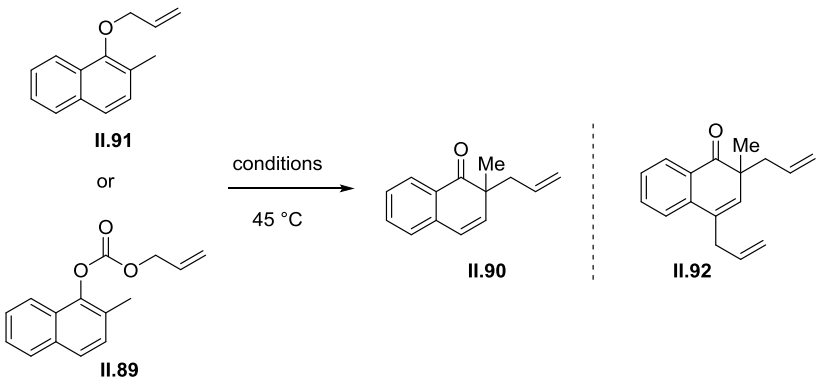
^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.7, 160.0 (d, *J* = 252.0 Hz), 150.3 (d, *J* = 4.1 Hz), 133.6, 130.0 (d, *J* = 4.6 Hz), 127.6 (d, *J* = 1.4 Hz), 126.3 (d, *J* = 8.4 Hz), 125.3 (d, *J* = 1.4 Hz), 125.2 (d, *J* = 17.1 Hz), 118.6 (d, *J* = 4.2 Hz), 117.7, 117.1 (d, *J* = 5.5 Hz), 110.6 (d, *J* = 19.8 Hz), 76.3, 43.2, 39.3, 14.2, 13.0.

HRMS (EI) calcd for $C_{18}H_{20}O_2NF$ $[M]^+$: 301.1473; found: 301.1480.

10.2.2.3 Screenings for the CADA Reaction

General Procedure for the Racemic Dearomatization with $Pd(PPh_3)_4$:

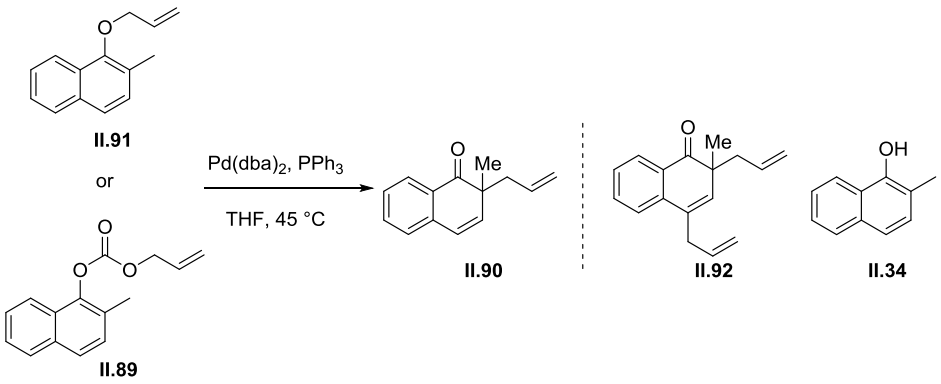
A Schlenk tube was charged with tetrakis(triphenylphosphine)palladium(0) (0.100 equiv) and purged with argon three times. The substrate **II.91** or **II.89** (1 equiv) was added as a 0.05 M solution in the indicated solvent and the reaction mixture was heated to 45°C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel.



entry	catalyst[a]	solvent[b]	result with II.89	ratio of II.90 : II.92[f]	result with II.91	ratio of II.90 : II.92[f]
1	$Pd(PPh_3)_4$	THF	**II.89** + **II.92** (61%)[e]	1 : 0.22	-	-
2	$Pd(PPh_3)_4$	*n*-hexane/ toluene (1:10)	**II.91**	-	**II.91**	-
3	$Pd(PPh_3)_4$	1,4-dioxane[c]	**II.89** + **II.92** (37%)[e]	1 : 0.14	**II.90** + **II.92** (45%)[e]	1 : 0.24
4	$Pd(PPh_3)_4$	1,4-dioxane	**II.89** + **II.92** (15%)[e]	1 : 1.1	**II.90** + **II.92** (38%)[e]	1 : 0.50
5	$Pd(PPh_3)_4$	THF[d]	**II.89** + **II.92** (48%)[e]	1 : 0.20	**II.90** + **II.92** (47%)[e]	1 : 0.27
6	$Pd(PPh_3)_4$	CH_2Cl_2	**II.89** + **II.92** (28%)[e]	1 : 1.6	**II.90** + **II.92** (34%)[e]	1 : 0.92

[a] 10 mol% catalyst were used; [b] solvents were degassed via freeze-pump-thaw; 0.04 M; [c] not degassed; [d] 0.02 M solution; [e] isolated as an inseparable mixture; [f] determined by ^{1}H NMR spectroscopy.

General Procedure for the Racemic Dearomatization with $Pd(dba)_2/PPh_3$:

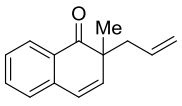


A Schlenk tube was charged with bis(dibenzylideneacetone)palladium (II) (0.102 equiv) and triphenylphosphine (0.5 equiv) and purged with argon three times. The substrate **II.91** or **II.89** (1 equiv) was added as a 0.05 M solution in degassed tetrahydrofuran and the reaction mixture was heated to 45°C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated.

General Procedures for the CADA Reaction:

For the screening with chiral ligands to obtain enantiomerically enriched material, the experiments were carried out using procedures **A–H** and the following HPLC parameters for the determination of the *ee*:

Chiral HPLC:	Retention time **II.90a**: 7.07 min
	Retention time **II.90b**: 7.60 min
Column:	CHIRALCEL® 5 µm OB-H column
Flow rate:	1 mL/min
Mobile phase:	100% *n*-heptane
Temperature:	40 °C
Wavelength:	230 nm



II.90

Analytical data for II.90:

TLC (20% diethyl ether in hexanes), R_f = 0.40 (ANIS, UV).

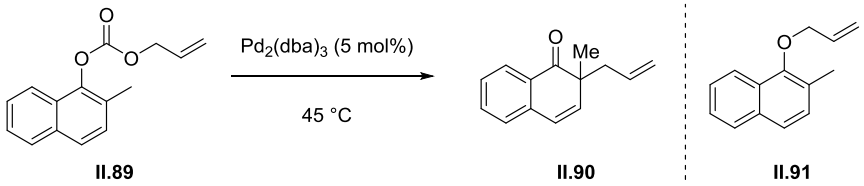
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.05 (ddt, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.59 (d, *J* = 9.8 Hz, 1H), 6.10 (d, *J* = 9.7 Hz, 1H), 5.58 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.01 (ddt, *J* = 17.0, 2.0, 1.4 Hz, 1H), 4.93 (ddt, *J* = 10.1, 1.9, 0.9 Hz, 1H), 2.67 (ddt, *J* = 13.6, 7.4, 1.1 Hz, 1H), 2.29 (ddt, *J* = 13.6, 7.2, 1.3 Hz, 1H), 1.27 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 203.09, 139.62, 138.49, 134.45, 133.49, 129.35, 127.95, 127.42, 127.10, 124.01, 118.15, 49.30, 44.64, 24.78.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928 (*w*), 1673 (*vs*), 1642 (*m*), 1598 (*s*), 1449 (*w*), 13.20 (*m*), 1268 (*m*), 1233 (*m*), 985 (*m*), 919 (*m*), 792 (*vs*), 693.2 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{14}O$ $[M]^+$: 198.1039; found: 198.1043.

Procedure A: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) (3.78 mg, 4.13 μmol, 0.050 equiv) and a chiral ligand (0.11 equiv) and was afterwards purged with argon one time. (Degassed) solvent was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl carbonate **II.89** (20.0 mg, 82.6 mmol, 1 equiv) in the (degassed) solvent was added and the reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes). The *ee* of the clean product **II.90** was analyzed by chiral HPLC.

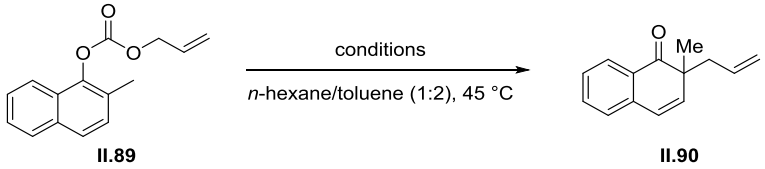


II.89 **II.90** **II.91**

entry	ligand	solvent[a]	result[b]	*ee* [%]
1	(*S*,*S*)-**L3**	THF	**II.91**	-
2	(*S*,*S*)-**L3**	toluene	**II.91**	-
3	(*S*,*S*)-**L3**	*n*-hexane/toluene (1:2)	**II.91**	-
4	(*S*,*S*)-**L3**	MTBE	**II.91**	-
5	(*S*,*S*)-**L3**	DME	**II.91**	-
6	(*R*)-**L5**	THF	**II.90** (23%)	6
7	(*R*)-**L5**	toluene	**II.90** (14%)	8
8	(*R*)-**L5**	*n*-hexane/toluene (1:2)	**II.90** (trace)	-
9	(*R*)-**L5**	MTBE	**II.90** (trace)	-
10	(*R*)-**L5**	DME	**II.90** (9%)	-
11	(*S*,*S*)-**L1**	THF	**II.90** (12%)	58
12	(*S*,*S*)-**L1**	toluene	**II.90** (18%)	70
13	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)	**II.90** (31%)	60
14	(*S*,*S*)-**L1**	MTBE	**II.90** (24%)	62
15	(*S*,*S*)-**L1**	DME	**II.90** (trace)	-
16	(*S*,*S*)-**L1**	benzene[c]	**II.90** (70%)	42
17	(*S*,*S*)-**L1**	chlorobenzene[c]	**II.90** (60%)	42
18	(*S*,*S*)-**L1**	pyridine[c]	**II.90** (24%)	46
19	(*S*,*S*)-**L1**	trifluorotoluene[c]	**II.90** (15%)	46
20	(*S*,*S*)-**L1**	toluene[c]	**II.90** (18%)	66
21	(*R*,*R*)-**L6**	benzene[c]	**33 + 35** (trace)[d]	-
22	(*R*,*R*)-**L6**	toluene[c]	**33 + 35** (trace)[d]	-
23	(*R*,*R*)-**L6**	THF[c]	**33 + 35** (trace)[d]	-
24	(*S*,*S*)-**L7**	benzene[c]	**II.89, II.91** (trace)[d]	70
25	(*S*,*S*)-**L7**	toluene[c]	**II.89, II.91** (trace)[d]	71
26	(*S*,*S*)-**L7**	chlorobenzene[c]	**II.89, II.91** (trace)[d]	70
27	(*S*,*S*)-**L7**	*n*-hexane/toluene (1:2) [c]	**II.90** (12%)	69

[a] solvents were degassed via freeze-pump-thaw; [b] refer to isolated yields; [c] solvents were not degassed; [d] determined by crude ^{1}H NMR.

Procedure B: The reaction was carried out at a concentration of 0.04 M. A Schlenk tube was charged with tris(dibenzylideneacetone) dipalladium(0) and a chiral ligand and was afterwards purged with argon one time. A degassed solvent mixture of *n*-hexane/toluene (1:2) was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl carbonate **II.89** (20.0 mg, 82.6 mmol, 1 equiv) in the degassed solvent mixture of *n*-hexane/toluene (1:2) was added and the reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes). The *ee* of the clean product **II.90** was analyzed by chiral HPLC.

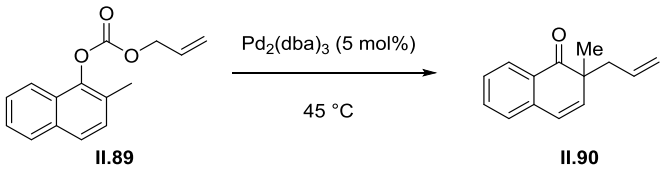


II.89 **II.90**

entry	catalyst	ligand	result	*ee*[a]
1	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (11 mol%)	**II.90** (31%)	60%
2	$Pd_2(dba)_3$ (10 mol%)	(*S*,*S*)-**L1** (22 mol%)	**II.90** (55%)	50%
3	$Pd_2(dba)_3$ (100 mol%)	(*S*,*S*)-**L1** (200 mol%)	**II.90** (49%)	32%

[a] determined by chiral HPLC analysis; the solvents were degassed via freeze-pump-thaw; 0.04 M.

Procedure C: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with tris(dibenzylideneacetone) dipalladium(0) (3.78 mg, 4.13 μmol, 0.050 equiv) and the (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**) (6.27 mg, 9.08 μmol, 0.110 equiv) and was afterwards purged with argon one time. (Degassed) solvent was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl carbonate **II.89** (20.0 mg, 82.6 mmol, 1 equiv) in the (degassed) solvent was added, followed by subsequent addition of the additive. The reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes).

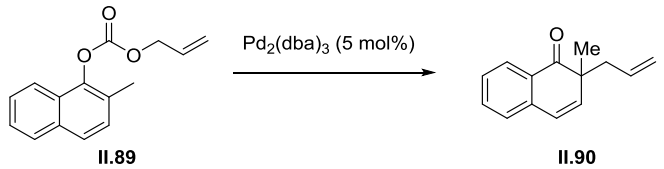


II.89 II.90

entry	ligand[a]	solvent[b]	additive	result	*ee* [%][c]
1	(*S*,*S*)-**L1**	benzene	LiCl (1 equiv)	**II.90** (83%)	44
2	(*S*,*S*)-**L1**	benzene	DBU (0.1 equiv)	**II.90** (28%)	68

[a] 11 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] determined by chiral HPLC analysis.

Procedure D: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with tris(dibenzylideneacetone) dipalladium(0) (3.78 mg, 4.13 μmol, 0.050 equiv) and the (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**) (6.27 mg, 9.08 μmol, 0.110 equiv) and was afterwards purged with argon one time. (Degassed) solvent was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl carbonate **II.89** (20.0 mg, 82.6 mmol, 1 equiv) in the (degassed) solvent was added and the reaction was stirred at the indicated temperature. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes).



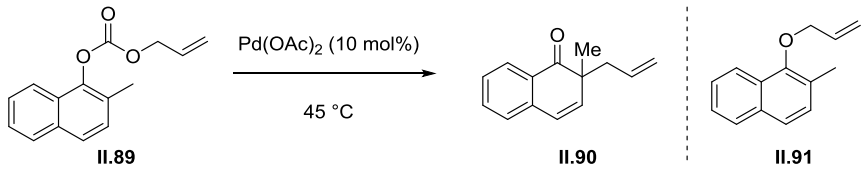
II.89 II.90

entry	ligand[a]	solvent[b]	T [°C]	result	*ee* [%][c]
1	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)[d]	60	**II.90** (67%)	44
2	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)	60	**II.90** (67%)	52
3	(*S*,*S*)-**L1**	benzene	23	**II.90** (26%)	64

[a] 11 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] determined by chiral HPLC analysis; [d] solvent was degassed via freeze-pump-thaw.

Procedure E: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with palladium(II) acetate (1.85 mg, 8.26 μmol, 0.100 equiv) and the (*S*,*S*)-DACH-

phenyl Trost ligand ((*S*,*S*)-**L1**) (5.70 mg, 8.26 μmol, 0.100 equiv) and was afterwards purged with argon one time. (Degassed) solvent was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl carbonate **II.89** (20.0 mg, 82.6 mmol, 1 equiv) in the (degassed) solvent was added and the reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes).

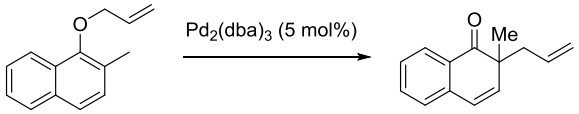


1	ligand[a]	solvent[b]	result[c]
1	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)[d]	**II.90** (8%) + **II.91** (40%)
2	(*S*,*S*)-**L1**	*n*-hexane/toluene (1:2)	**II.90** (11%) + **II.91** (46%)
3	(*S*,*S*)-**L1**	benzene	**II.90** (11%) + **II.91** (51%)
4	(*S*,*S*)-**L1**	chlorobenzene	**II.90** (12%) + **II.91** (71%)
5	(*S*,*S*)-**L1**	toluene	**II.90** (17%) + **II.91** (83%)
6	(*S*,*S*)-**L1**	1,4-dioxane	**II.90** (21%) + **II.91** (57%)
7	(*S*,*S*)-**L1**	1,2-dichloroethane	**II.90** (9%) + **II.91** (72%)
8	(*S*,*S*)-**L1**	trifluorotoluene	**II.90** (6%) + **II.91** (62%)
9	(*S*,*S*)-**L1**	CPME[d]	**II.90** (2%) + **II.91** (6%) + **II.89** (69%)
10	(*S*,*S*)-**L1**	DME[d]	**II.90** (15%) + **II.91** (67%) + **II.89** (6%)
11	(*S*,*S*)-**L1**	CH_3CN[d]	**II.90** (8%) + **II.91** (70%)
12	(*S*,*S*)-**L1**	CH_2Cl_2	**II.90** (41%) + **II.91** (47%)
13	(*S*,*S*)-**L1**	CH_2Cl_2[d]	**II.90** (20%) + **II.91** (62%)

[a] 10 mol% ligand were used; [b] solvents were not degassed; 0.05 M; [c] yield was determined by ^{1}H NMR ($CDCl_3$, 400 or 600 MHz, dimethyl sulfone-d_6 as internal standard); [d] solvents were degassed via freeze-pump-thaw.

Procedure F: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) (4.62 mg, 5.04 μmol, 0.050 equiv) and a chiral ligand (0.11 equiv) and was afterwards purged with argon one time. (Degassed) solvent was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl naphthol ether **II.91** (20.0 mg, 0.101 mmol, 1 equiv) in the (degassed) solvent was added and the reaction was

stirred at the indicated temperature. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes). The *ee* of the clean product **II.90** was analyzed by chiral HPLC.

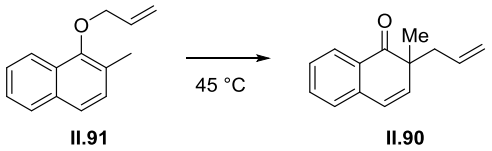


II.91 **II.90**

entry	ligand[a]	solvent[b]	T [°C]	result [%][c]	*ee* [%][d]
1	(*S*,*S*)-**L1**	benzene	45	**II.90**: 88 (84)	59
2	(*S*,*S*)-**L1**	benzene[e]	45	**II.90**: 84 (76)	-
3	(*S*,*S*)-**L1**	benzene	35	**II.90**: 69 (68)	60
4	(*S*,*S*)-**L1**	benzene	23	**II.90**: 62 (57)	62
5	(*S*,*S*)-**L3**	benzene	45	**II.91**	-
6	(*S*,*S*)-**L3**	1,4-dioxane	45	**II.91**	-
7	(*S*,*S*)-**L7**	benzene	45	**II.90**: 17 (16)	78
8	(*S*,*S*)-**L7**	benzene[e]	45	**II.90**: 18	-
9	(*S*,*S*)-**L7**	1,4-dioxane	45	**II.90**: 25 (24)	73
10	(*S*,*S*)-**L7**	1,4-dioxane[e]	45	**II.90**: 18	-
11	(*R*)-**L8**[f]	THF[e]	45	**II.90**: (19)	0

[a] 11 mol% ligand was used; [b] solvents were not degassed; 0.05 M; [c] yield was determined by ^{1}H NMR ($CDCl_3$, 400 or 600 MHz, dimethyl sulfone-d_6 as internal standard); yield in parentheses refer to isolated yield; [d] determined by chiral HPLC analysis of the isolated product; [e] solvents were degassed via freeze-pump-thaw; [f] 12.5 mol% ligand were used.

Procedure G: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) and the (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**) and was afterwards purged with argon one time. (Degassed) benzene was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl naphthol ether **II.91** (20.0 mg, 0.101 mmol, 1 equiv) in the (degassed) benzene was added and the reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes). The *ee* of the clean product **II.90** was analyzed by chiral HPLC.

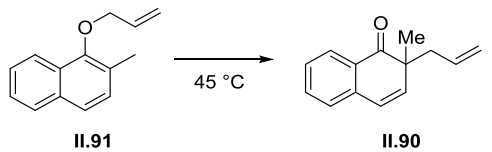


II.91 **II.90**

entry	catalyst	ligand	solvent[a]	result [%][b]	*ee* [%][c]
1	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (10 mol%)	benzene[d]	**II.90**: 72 (76)	53
2	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (9 mol%)	benzene[d]	**II.90**: traces	-
3	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (9 mol%)	benzene	**II.90**: 36 (33)	60
4	$Pd_2(dba)_3$ (5 mol%)	(*S*,*S*)-**L1** (8 mol%)	benzene[d]	**II.91**	-
5	$Pd_2(dba)_3$ (4 mol%)	(*S*,*S*)-**L1** (8.8 mol%)	benzene	**II.90**: 85 (87)	49
6	$Pd_2(dba)_3$ (3 mol%)	(*S*,*S*)-**L1** (6.6 mol%)	benzene[d]	**II.90**: 76	-
7	$Pd_2(dba)_3$ (3 mol%)	(*S*,*S*)-**L1** (6.6 mol%)	benzene	**II.90**: 66 (56)	61

[a] solvents were not degassed; 0.05 M; [b] yield was determined by ^{1}H NMR ($CDCl_3$, 400 or 600 MHz, dimethyl sulfone-d_6 as internal standard); yields in parentheses refer to isolated yields; [c] determined by chiral HPLC analysis of the isolated product; [d] solvents were degassed via freeze-pump-thaw.

Procedure H: The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with the catalyst (0.100 equiv) and the chiral ligand (0.110 equiv) and was afterwards purged with argon one time. (Degassed) solvent was added and the catalyst was stirred at 23 °C for 30 min. A solution of the allyl naphthol ether **II.91** (20.0 mg, 0.101 mmol, 1 equiv) in the (degassed) solvent was added and the reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in hexanes). The *ee* of the clean product **II.90** was analyzed by chiral HPLC.



II.91 **II.90**

entry	catalyst[a]	ligand[b]	solvent[c]	result[d]	*ee* [%][d]
1	$Pd(OAc)_2$	(*S*,*S*)-**L1**	benzene	**II.91**	-
2	$Pd(OAc)_2$	(*S*,*S*)-**L1**	benzene/CH_2Cl_2	**II.91**	-
3	$Pd(OAc)_2$	(*S*,*S*)-**L1**	CH_2Cl_2	**II.91**	-
4	$Pd(OAc)_2$	(*S*,*S*)-**L1**	THF	**II.91**	-

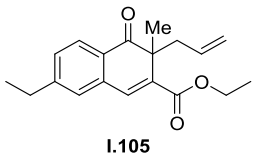
5	Pd(*t*-$Bu_3P)_2$	(*S*,*S*)-**L1**	benzene	**II.91**	-
6	$Pd(dppe)_2$	(*S*,*S*)-**L1**	benzene	**II.91**	-
7	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	benzene	**II.90** (41%)	60
8	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	benzene[e]	**II.90** (63%)	60
9	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	toluene	**II.90** (68%)	57
10	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	toluene[e]	**II.90** (47%)	55
11	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	1,4-dioxane	**II.90** (55%)	55
12	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	THF	**II.90** (traces)	-
13	$Pd(dmdba)_2$	(*S*,*S*)-**L1**	1,2-dichlorobenzene	**II.90** (60%)	48
14	$Pd(dmdba)_2$	(*S*,*S*)-**L7**	benzene	**II.91**	-
15	$Pd(dmdba)_2$	(*S*,*S*)-**L7**	toluene	**II.91**	-
16	$Pd(dmdba)_2$	(*S*,*S*)-**L7**	1,4-dioxane	**II.91**	-

[a] 10 mol% catalyst were used; [b] 11 mol% ligand was used; [c] solvents were not degassed; 0.05 M; [d] determined by chiral HPLC analysis of the isolated product; [e] solvents were degassed via freeze-pump-thaw. dmdba = 3,5,3',5'-dimethoxydibenzylideneacetone.

10.2.2.4 Substrate Scope

General Procedure for the Substrate Scope:

The reaction was carried out at a concentration of 0.05 M. A Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) (0.0500 equiv) and the (*S*,*S*)-DACH-phenyl Trost ligand ((*S*,*S*)-**L1**) (0.110 equiv) and was afterwards purged with argon one time. Benzene was added and the catalyst was stirred at 23 °C for 30 min. A solution of the substrate (0.101 mmol, 1 equiv) in benzene was added and the reaction was heated to 45 °C in a preheated oil bath. After TLC indicated no further conversion, the crude mixture was diluted with diethyl ether, filtered through a small plug of silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel. The *ee* of the clean substrate was analyzed by chiral HPLC.



I.105

Following the general procedure, allylated naphthol **I.106** (30.1 mg, 0.101 mmol) provided the ketone **I.105** (28.4 mg, 94%) as a colorless oil after flash column chromatography on silica gel (5% diethyl ether in hexanes).

Analytical data for I.105:

TLC (33% ethyl acetate in hexanes), R_f = 0.69 (UV, CAM, $KMnO_4$).

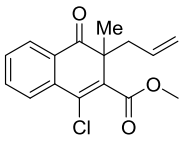
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 7.9 Hz, 1H), 7.71 (s, 1H), 7.35 – 7.31 (m, 1H), 7.23 (d, *J* = 1.7 Hz, 1H), 5.42 – 5.28 (m, 1H), 4.89 (ddt, *J* = 17.0, 2.5, 1.4 Hz, 1H), 4.77 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1H), 4.30 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.06 (ddt, *J* = 13.6, 8.1, 1.1 Hz, 1H), 2.90 (ddt, *J* = 13.6, 6.6, 1.3 Hz, 1H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.51 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.8, 165.8, 151.7, 137.6, 135.9, 134.6, 134.1, 130.3, 128.8, 127.8, 127.6, 117.4, 60.9, 51.6, 43.0, 29.2, 25.1, 15.1, 14.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*w*), 1933 (*w*), 1709 (*s*), 1672 (*s*), 1599 (*m*), 1452 (*w*), 1374 (*w*), 1279 (*m*), 1243 (*m*), 1215 (*vs*), 1094 (*w*), 1043 (*m*), 982 (*m*), 919 (*m*), 847 (*m*), 776 (*m*), 702 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1563; found: 298.1568.

Chiral HPLC:	Retention time **I.105a**: 5.82 min
	Retention time **I.105b**: 7.90 min
Column:	CHIRALCEL® 5 μm OB-H column
Flow rate:	1 mL/min
Mobile phase:	*n*-heptane:MTBE = 90:10 (v/v)
Temperature:	40 °C
Wavelength:	230 nm



II.95

Following the general procedure, allylated naphthol **II.107** (29.4 mg, 0.101 mmol) provided the ketone **II.95** (25.7 mg, 88%) as a colorless oil after flash column chromatography on silica gel (5% diethyl ether in hexanes).

Analytical data for II.95:

TLC (33% ethyl acetate in hexanes), R_f = 0.65 (UV, CAM, $KMnO_4$).

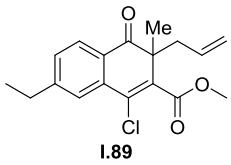
^{1}H NMR (599 MHz, $CDCl_3$) δ: 8.06 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.86 (d, *J* = 7.4 Hz, 1H), 7.70 (td, *J* = 7.7, 1.6 Hz, 1H), 7.53 – 7.48 (m, 1H), 5.58 – 5.49 (m, 1H), 4.99 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.91 – 4.85 (m, 1H), 3.91 (s, 3H), 2.79 – 2.73 (m, 1H), 2.58 – 2.51 (m, 1H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.8, 166.5, 137.9, 134.8, 134.5, 132.2, 130.2, 129.8, 127.6, 127.3, 126.2, 119.1, 52.8, 52.5, 44.4, 23.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3076 (*w*), 2952 (*w*), 1728 (*vs*), 1681 (*s*), 1594 (*m*), 1452 (*m*), 1434 (*m*), 1312 (*m*), 1282 (*vs*), 1258 (*s*), 1246 (*s*), 1224 (*s*), 1194 (*m*), 1111 (*m*), 1044 (*m*), 988 (*m*), 949 (*m*), 924 (*m*), 848 (*m*), 766 (*s*), 695 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{15}O_3{}^{35}Cl$ $[M]^+$: 290.0704; found: 290.0709.

Chiral HPLC:	Retention time **II.95a**: 12.33 min
	Retention time **II.95b**: 21.26 min
Column:	CHIRALCEL® 5 µm OD-H column
Flow rate:	1 mL/min
Mobile phase:	*n*-heptane:MTBE = 95:5 (v/v)
Temperature:	40 °C
Wavelength:	230 nm



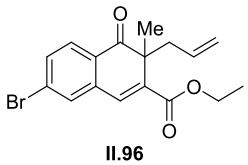
I.89

Following the general procedure, allylated naphthol **I.88** (30.9 mg, 0.101 mmol) provided the ketone **I.89** (28.1 mg, 88%) as a colorless oil after flash column chromatography on silica gel (5% diethyl ether in hexanes).

For the analytical data, except the ones of the chiral HPLC, see the experimental procedure for salimabromide.

Analytical data for I.89:

Chiral HPLC:	Retention time **I.89a**: 10.01 min
	Retention time **I.89b**: 12.56 min
Column:	CHIRALCEL® 5 µm OD-H column
Flow rate:	1 mL/min
Mobile phase:	*n*-heptane:MTBE = 95:5 (v/v)
Temperature:	40 °C
Wavelength:	254 nm



II.96

Following the general procedure, allylated naphthol **II.106** (34.9 mg, 0.101 mmol) provided the ketone **II.96** (28.9 mg, 83%) as a light yellow oil after flash column chromatography on silica gel (5% diethyl ether in hexanes).

Analytical data for II.96:

TLC (33% ethyl acetate in hexanes), R_f = 0.55 (CAM, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 8.3 Hz, 1H), 7.63 (s, 1H), 7.61 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 5.34 (dddd, *J* = 16.9, 10.1, 8.0, 6.7 Hz, 1H), 4.89 (dq, *J* = 17.0, 1.4 Hz, 1H), 4.79 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1H), 4.30 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.06 (ddt, *J* = 13.5, 8.0, 1.0 Hz, 1H), 2.88 (ddt, *J* = 13.6, 6.7, 1.3 Hz, 1H), 1.51 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.3, 165.4, 139.3, 137.2, 133.6, 133.5, 132.7, 132.0, 129.8, 129.0, 128.3, 117.9, 61.1, 51.9, 43.1, 24.9, 14.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2980 (*w*), 2361 (*w*), 2333 (*w*), 1714 (*vs*), 1678 (*s*), 1636 (*w*), 1583 (*m*), 1560 (*m*), 1457 (*w*), 1374 (*w*), 1269 (*s*), 1243 (*m*), 1213 (*s*), 1045 (*m*), 983 (*w*), 921 (*w*), 777 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{17}O_3{}^{79}Br$ $[M]^+$: 348.0356; found: 348.0351.

10.2.3 Claisen Rearrangement of Allyl Chlorovinyl Ether

10.2.3.1 Synthesis of Precursors

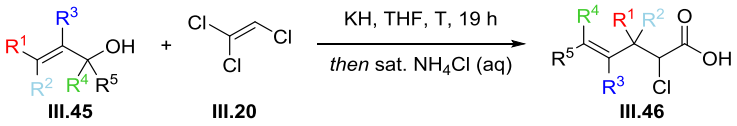
For the synthesis of **III.55** see H. Liu, A. Chatterjee, D. C. Tully, P. B. Alper, B. Bursulaya, J. Guo, D. Woodmansee, D. Mutnick, D. S. Karanewsky, Y. He, Inhibitors of Chatepsin S, PCT Int. Appl. 2005/034848 A2, 21 April 2005 and T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 13652–13655.

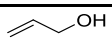
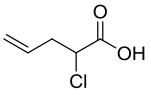
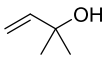
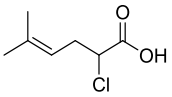
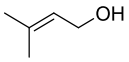
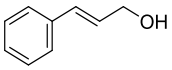
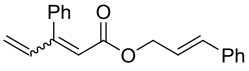
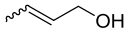
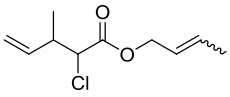
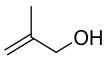
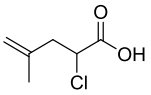
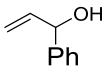
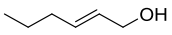
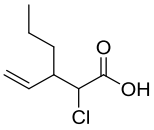
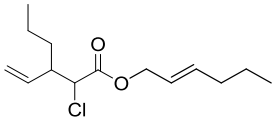
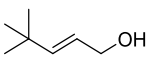
10.2.3.2 Screenings for the Synthesis of α-Chloro-4-enoic Acids

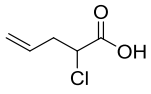
General Procedures for the Claisen Reaction:

For the screenings to obtain α-chloro-4-enoic acids, the experiments were carried out using procedures **A–D**.

Procedure A: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol (1 equiv) in tetrahydrofuran (0.75 M) was added at 0 °C. After 35 min, the reaction was cooled to the indicated temperature, trichloroethene (**III.20**) (1.2 equiv) in tetrahydrofuran (0.8 M) was added over 15 min and the reaction was allowed to warm to 23 °C. After 19 h, saturated aqueous ammonium chloride solution was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.

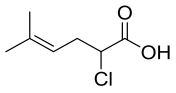


entry	substrate	T	result
1	 III.41	−70 to 23 °C	 III.44
2	 III.48	−70 to 23 °C	 III.56
3	 III.49	−70 to 23 °C	-
4	 III.50	−70 to 23 °C	 III.57
5	 III.51	−85 to 23 °C	 III.58
6	 III.52	−50 to 23 °C	 III.59
7	 III.53	−50 to 23°C	-
8	 III.54	−50 to 23 °C	 III.60  III.61
9	 III.55	−50 to 23 °C	-


III.44

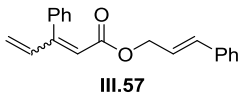
Following the general procedure, allyl alcohol (**III.41**) provided α-chlorinated acid **III.44**.

The obtained analytical data for **III.44** were in full agreement with those reported in the literature.[203]


III.56

Following the general procedure, 2-methylbut-3-en-2-ol (**III.48**) provided α-chlorinated acid **III.56**.

The structure was unambiguously identified by converting **III.56** into the corresponding dienoic acid **III.65** (*vide supra*).


III.57

Following the general procedure, cinnamyl alcohol (**III.50**) provided dienoic ester **III.57**.

Analytical data for III.57:

Note: Since purification was only partially possible, the structure was determined by impure material.

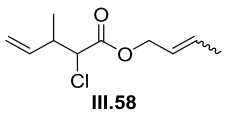
TLC (20% diethyl ether in hexanes), R_f = 0.86 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (dd, *J* = 17.6, 10.8 Hz, 1H), 7.41 – 7.29 (m, 10), 6.68 (d, *J* = 15.9 Hz, 1H), 6.33 (dt, *J* = 15.7, 6.4 Hz, 1H), 5.85 (s, 1H), 5.61 (d, *J* = 10.8 Hz, 1H), 5.32 (d, *J* = 17.6 Hz, 1H), 4.82 (d, *J* = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.0, 156.4, 139.6, 136.5, 134.3, 133.9, 129.2, 128.8, 128.8, 128.4, 128.2, 126.8, 125.6, 123.6, 118.1, 65.0.

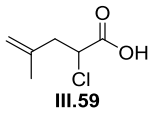
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3027 (*w*), 2924 (*w*), 1711 (*m*), 1621 (*w*), 1583 (*m*), 1447 (*w*), 1375 (*w*), 1344 (*w*), 1276 (*m*), 1154 (*vs*), 1110 (*w*), 1001 (*w*), 964 (*m*), 869 (*w*), 692 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{18}O_2$ $[M]^+$: 290.1301; found: 290.1302


III.58

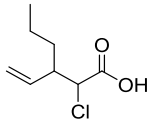
Following the general procedure, a diastereomeric mixture of crotyl alcohol (**III.51**) provided α-chlorinated ester **III.58**.

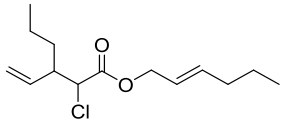
The structure was unambiguously identified by converting **III.58** into the corresponding dienoic acids **III.66a** and **III.66b** (*vide supra*).


III.59

Following the general procedure, 2-methylprop-2-en-1-ol (**III.52**) provided α-chlorinated acid **III.59**.

The structure was unambiguously identified by converting **III.59** into the corresponding dienoic acid **III.64** (*vide supra*).


III.60


III.61

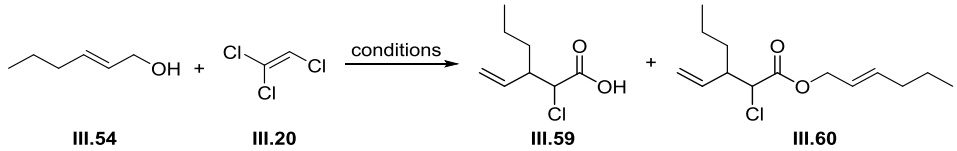
Following the general procedure, (*E*)-hex-2-en-1-ol (**III.54**) provided acid **III.60** and ester **III.61** as a 1.4 : 1 mixture.

The structure of acid **III.60** was unambiguously identified by converting the mixture **III.60** and **III.61** into the corresponding dienoic acids **III.62a** and **III.62b** (*vide supra*). The NMR spectrum of the reaction mixture was discussed in Chapter III.8.1.

Procedure B1: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol **III.54** in tetrahydrofuran (0.75 M) was added at 0 °C and the reaction was warmed to 23 °C. After 30 min, the reaction was cooled to the indicated temperature, trichloroethene (**III.20**) in tetrahydrofuran (0.8 M) was added over 10 min and the reaction was allowed to warm to 23 °C. After 19 h, water and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×) and dichloromethane (1 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.

Procedure B2: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol **III.54** (1 equiv) in tetrahydrofuran (0.75 M) was added at 0 °C and the reaction was warmed to 23 °C. After 30 min, the reaction mixture was added to a cooled solution of trichloroethene (**III.20**) in tetrahydrofuran (0.8 M) and the reaction was allowed to warm to 23 °C. After 19 h, water and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×) and dichloromethane (1 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate,

the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.



III.54 **III.20** **III.59** **III.60**

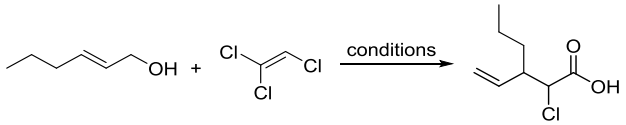
entry	conditions[a]	comment	result[b],[c]
1	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to 23 °C		**III.59** (34%), d.r. = 4.3 : 1 **III.60** (26%), d.r. = 1.4 : 1
2	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to 23 °C	ratio **III.54** : KH : **III.20** = 1 : 2.4 : 2	**III.59** (8%), d.r. = 1.4 : 1 **III.60** (9%), d.r. = 0.9 : 1
3	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, –78 °C to 23 °C		**III.59** (15%), d.r. = 1.2 : 1 **III.60** (13%), d.r. = 1 : 1
4	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to 23 °C	ratio **III.54** : KH : **III.20** = 3 : 2.4 : 1.2	**III.60** (39%), d.r. = 1 : 1
5	KH, **III.54**, 23 °C, *then* **III.20**, –78 °C to 23 °C		**III.59** (13%) **III.60** (9%), d.r. = 1.2 : 1
6	KH, **III.20**, 23 °C, *then* mixture added to **III.20**, 0 °C	ratio **III.54** : KH : **III.20** = 1 : 1 : 1	**III.60** (30%)

[a] ratio **III.54** : KH : **III.20** = 1 : 2.4 : 1.2 unless otherwise noted; [b] the yield was determined by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz; mesitylene as internal standard); [c] d.r. = *anti* : *syn*.

Procedure C1: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol **III.54** (1 equiv) in tetrahydrofuran (0.75 M) was

added at 0 °C and the reaction was warmed to 23 °C. After 30 min, the reaction was cooled to the indicated temperature, trichloroethene (**III.20**) (1.2 equiv) in tetrahydrofuran (0.8 M) was added over 10 min and the reaction was allowed to warm to −27 °C. After 2.5 h at this temperature, aqueous H_2SO_4 (10%, 1.2 equiv) was added and the reaction was warmed to 23 °. After 4.5 h, water and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×) and dichloromethane (1 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.

Procedure C2: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol **III.54** in tetrahydrofuran (0.75 M) was added at 0 °C and the reaction was warmed to 23 °C. After 30 min, the reaction mixture was added to a −78 °C cold solution of trichloroethene (**III.20**) in tetrahydrofuran (0.8 M) and the reaction was allowed to warm to −27 °C. After the indicated time at this temperature, aqueous H_2SO_4 (10%) or dry methanol (3.0 equiv) or hexafluoroisopropanol (3.0 equiv) was added and the reaction was warmed to 23 °. After 2–6 h, water and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×) and dichloromethane (1 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.

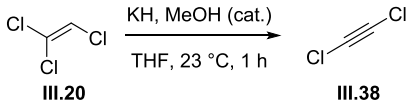


III.54 **III.20** **III.60**

entry	conditions[a]	comment	result[b],[c]
1	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C, *then* H_2SO_4 (10%), 23 °C		**III.60** (13%), d.r. = 19 : 1
2	KH, **III.54**, 0 °C to 23 °C, *then* **III.20**, –78 °C to –27 °C, *then* H_2SO_4 (10%), 23 °C		**III.60** (14%), d.r. = 13.3 : 1

3	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 1 : 4 : 1.2 : 1.2	**III.60** (10%), d.r. = 99 : 1
4	1) KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 1.5 h at −27 °C, *then* H_2SO_4 (10%), 23 °C		**III.60** (25%), d.r. = 15.7 : 1
5	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 45 min at −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 1.8 : 2.4 : 1.2 : 1.2	**III.60** (28%), d.r. = 15.7 : 1
6	KH, **III.54**, 0 °C to 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 45 min at −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 2.4 : 2.4 : 1.2 : 1.2	**III.60** (37%), d.r. = 13.3 : 1
7	1) KH, **III.54**, 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 50 min at −27 °C, *then* H_2SO_4 (10%), 23 °C	**III.54** : KH : **III.20** : H_2SO_4 = 1 : 2.4 : 1.2 : 0.55	**III.60** (26%), d.r. = 99 : 1
8	KH, **III.54**, 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 50 min at −27 °C, *then* MeOH, 23 °C	3 equiv of MeOH	**III.54** and traces of **III.20**
9	KH, **III.54**, 23 °C, *then* mixture added to **III.20**, −78 °C to −27 °C; 50 min at −27 °C, *then* HFIP, 23 °C	3 equiv of HFIP	**III.54** and traces of **III.20**

[a] ratio **III.54** : KH : **III.20** : H_2SO_4 = 1 : 2.4 : 1.2 : 1.2 unless otherwise noted; [b] the yield was determined by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz; mesitylene as internal standard); [c] d.r. = *anti* : *syn*.



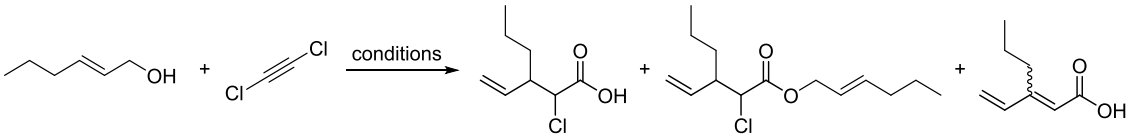
III.20 **III.38**

*Note: Dichloroacetylene (DCA, **III.38**) is highly toxic and explosive! All reactions were carried out behind a blast shield.*

Trichloroethene (**III.20**) (0.692 mL, 7.69 mmol, 1 equiv) and methanol (11.2 μL, 0.192 mmol, 0.0250 equiv) were added to a suspension of washed potassium hydride (401 mg, 10.0 mmol, 1.30 equiv) in tetrahydrofuran (7 mL). The reaction mixture was stirred for 1 h until gas evolution ceased. Stirring was stopped and the brown-grey supernatant was used immediately. It was assumed that the concentration of **III.38** is approximately 1 M.[204]

Procedure D1: A Schlenk tube was charged with washed potassium hydride or potassium *tert*-butoxide and tetrahydrofuran (1 M). A solution of allyl alcohol **III.54** in tetrahydrofuran (0.75 M) was added at 23 °C. After 30 min, the reaction was cooled to the indicated temperature, a solution of dichloroacetylene **III.38** (1 M in tetrahydrofuran) was added and the reaction was allowed to warm to 23 °C. After 3–6 h, saturated aqueous ammonium chloride solution and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×) and dichloromethane (1 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.

Procedure D2: A Schlenk tube was charged with washed potassium hydride (3 equiv), tetrahydrofuran (1 M) and methanol (2 equiv). After 30 min, the reaction mixture was cooled to 0 °C and a solution of dichloroacetylene **III.38** (1 M in tetrahydrofuran, 1 equiv) was added. After 15 min, allylic alcohol **III.54** (1 equiv) was added over 1.5 h (syringe pump) at 0 °C. After 3 h, saturated aqueous ammonium chloride solution and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×) and dichloromethane (1 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy. For analytical data of the isomeric mixture of **III.62a** and **III.62b** *vide supra*.



III.54 **III.38** **III.60** **III.61** **III.62a** (*E*) **III.62b** (*Z*)

entry	conditions	comment	result[a],[b]
1	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 1 : 1.1 : 2	**III.60** (34%), d.r. = 10 : 1 **III.61** (12%), d.r. = 1.5 : 1
2	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 1 : 1.1 : 3	**III.60** (30%)
3	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 1 : 0.1 : 3	**III.54** and traces of **III.61**
4	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 3 : 1.5 : 1	**III.61** (56%), d.r. = 1 : 1
5	KH, **III.54**, 23 °C, *then* **III.38**, 23 °C	ratio **III.54** : KH : **III.38** = 2 : 2 : 1	**III.61** (45%), d.r. = 1.1 : 1 **III.62** (18%), d.r. = 1 : 1.4[c]
6	*t*-BuOK, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : *t*-BuOK : **III.38** = 1.3 : 1 : 1.3	**III.61** (22%), d.r. = 1.3 : 1
7	KH, **III.54**, 23 °C, *then* **III.38**, −30 °C	ratio **III.54** : KH : **III.38** = 2 : 2 : 1	**III.60** (11%), d.r. = 6.14 : 1 **III.61** (8%), d.r. = 1 : 1.5 **III.62** (20%), d.r. = 1 : 1[c]
8	KH, MeOH, 23 °C, *then* **III.38**, 0 °C, *then* **III.54**, 0 °C (addition over 1.5 h)	ratio **III.54** : KH : **III.38** : MeOH = 1 : 3 : 1 : 2	**III.62** (33%), d.r. = 1 : 1.3[c]

[a] the yield was determined by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz; mesitylene as internal standard); [b] d.r. = *anti* : *syn*; [c] d.r. = *E* : *Z*.

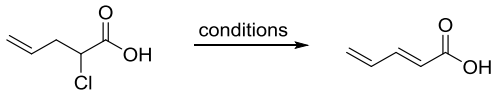
10.2.3.3 Screenings for the Synthesis of 2,4-Dienoic Acids

General Procedures for the Elimination Reaction

The screenings for the synthesis of 2,4-dienoic acids from α-chloro-4-enoic acids were carried out according to the procedures **A**-**B**.

Procedure A: A solution of **III.44** (1 equiv) in the indicated solvent (0.28 M) was added to the base in a pressure tube and the reaction mixture was heated to the indicated temperature. After the indicated time, water and aqueous hydrochloric acid solution (2 M or 37%) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.

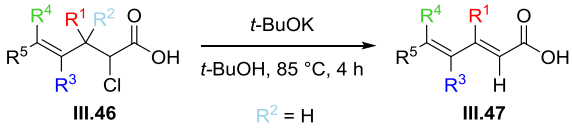
The obtained analytical data for **III.63** were in full agreement with those reported in the literature.[205]



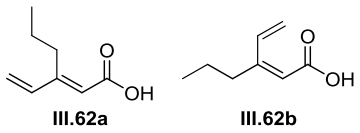
III.44 **III.63**

entry	base	conditions	result
1	*t*-BuOK (3.5 equiv)	*t*-BuOH, 85 °C, 5 h	**III.63**
2	*t*-BuOK (3.5 equiv)	*t*-BuOH, 50 °C, 4 h	**III.63**+ traces of **45**
3	DBU (3.5 equiv)	THF, 65 °C, 4 h	**III.44**
4	KOTMS (3.5 equiv)	THF, 85 °C, 4.5 h	**III.63** : **III.44** = 2 : 1[a]
5	*t*-BuOK (2.1 equiv)	*t*-BuOH, 85 °C, 4.5 h	**III.63** : **III.44** = 3 : 1[a]
6	*t*-BuOK (ca. 10 equiv)	*t*-BuOH, 23 °C, 4.5 h	**III.63** + traces of **III.44**
7	NaOH (3.5 equiv)	*i*-PrOH, 85 °C, 5 h	**III.63** : **III.44** = 6.7 : 1[a]

[a] ratio determined by ^{1}H NMR spectroscopy.



Procedure B: A solution of **III.46** (1 equiv) in the *tert*-butanol (0.28 M) was added to potassium *tert*-butoxide (3.5 equiv) in a pressure tube and the reaction mixture was heated to 85 °C. After 4 h, water and aqueous hydrochloric acid solution (37%) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel. The d.r. of the product was analyzed by ^{1}H NMR spectroscopy.



Following the general procedure, a mixture of α-chlorinated acid **III.60** and ester **III.61** provided a mixture of dienes **III.62a** and **III.62b** (d.r. = 1 : 3.5) as a light brown solid without purification.

Analytical data for III62a and III.62b:

Note: Since purification was not possible, the structure was determined by impure material. Signals marked with an asterisk belong to the Z-isomer ***III.62b****.*

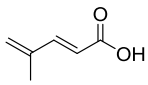
TLC (20% diethyl ether in hexanes), R_f = 0.41 (smear, $KMnO_4$).

^{1}H NMR (599 MHz, $CDCl_3$) δ. 11.43 (s, 1H), 7.70 (ddd, *J* = 17.7, 11.1, 0.8 Hz, 1H)*, 6.34 (dd, *J* = 17.4, 10.7 Hz, 0.3H), 5.79 (s, 0.2H), 5.73 (s, 1H)*, 5.67 (d, *J* = 17.4 Hz, 0.3H), 5.65 (d, *J* = 17.7 Hz, 1H)*, 5.48 (dt, *J* = 11.1, 1.4 Hz, 1H)*, 5.42 (d, *J* = 10.7 Hz, 0.3H), 2.80 – 2.74 (m, 0.5H), 2.39 – 2.32 (m, 2H)*, 1.56 (dq, *J* = 15.1, 7.5 Hz, 2H)*, 1.52 (td, *J* = 14.7, 7.1 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 1.5H), 0.96 (t, *J* = 7.4 Hz, 3H)*.

^{13}C NMR (151 MHz, $CDCl_3$) δ. 171.8, 171.5, 159.6, 157.6, 139.1, 133.1, 121.0, 120.2, 118.7, 116.5, 35.9, 29.2, 23.1, 22.4, 14.5, 14.1.

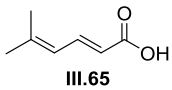
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (*m*), 2929 (*m*), 2872 (*m*), 1676 (*s*), 1621 (*m*), 1585 (*m*), 1456 (*w*), 1438 (*w*), 1400 (*w*), 1248 (*s*), 1183 (*s*), 1051 (*s*), 999 (*s*), 937 (*s*), 894 (*s*), 764 (*m*), 718 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{18}O_2$ $[M]^+$: 140.0832; found: 140.0837.


III.64

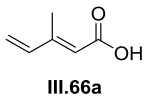
Following the general procedure, α-chlorinated acid **III.59** (50.0 mg, 0.336 mmol) provided diene **III.64** (22.6 mg, 60%) as a white solid after flash column chromatography on silica gel (14% ethyl acetate in hexanes).

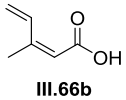
The obtained analytical data were in full agreement with those reported in the literature.[206]


III.65

Following the general procedure α-chlorinated acid **III.56** (23.0 mg, 0.141 mmol) provided diene **III.65** (3.2 mg, 18%) as a beige solid after flash column chromatography on silica gel (11% ethyl acetate and 1% acetic acid in hexanes).

The obtained analytical data were in full agreement with those reported in the literature.[207]


III.66a


III.66b

Following the general procedure, α-chlorinated ester **III.58** provided a mixture of dienes **III.66a** and **III.66b** (d.r. = 3 : 2) as a brown oil without purification.

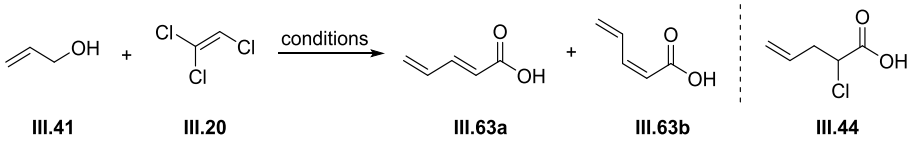
The obtained analytical data of the crude reaction mixture were in full agreement with those reported in the literature.[208]

General Procedures for the One-Pot Reaction

The screenings for the synthesis of 2,4-dienoic acids from allylic alcohols were carried out according to the procedures **A**-**B**.

Procedure A: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol (**III.41**) (1 equiv) in tetrahydrofuran (0.75 M) was added at 0 °C. After 35 min, the reaction was cooled to −50 °C, trichloroethene (**III.20**) (1.2 equiv) in tetrahydrofuran (0.8 M) was added and the reaction was allowed to warm to 23 °C. After 2 h, *tert*-butanol (0.28 M) or *iso*-propanol (0.28 M) and potassium *tert*-butoxide or sodium hydroxide (3.5 equiv) were added and the reaction mixture was heated to 85 °C. After the indicated time, water and aqueous hydrochloric acid solution (37%) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×). The combined organic

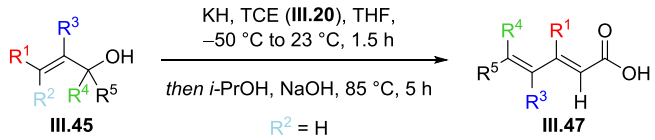
layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy.



III.41 **III.20** **III.63a** **III.63b** **III.44**

entry	conditions	ratio of **III.63a** : **III.44**[a]
1	1) KH, THF, −50 °C to 23 °C, 2.5 h 2) *t*-BuOK (3.5 equiv), 60 °C, 4.5 h	2.3 : 1; traces of **III.63b**
2	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (3.5 equiv), 80 °C, 4 h	5.3 : 1; traces of **III.63b**
3	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (3.5 equiv), 85 °C, 15 h	3.5 : 1; traces of **III.63b**
4	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (4 equiv), 85 °C, 15 h	2.7 : 1
5	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (2 equiv), 85 °C, 5 h	2.3 : 1; traces of **III.63b**
6	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *t*-BuOH, *t*-BuOK (1.5 equiv), 85 °C, 5 h	3 : 1; traces of **III.63b**
7	1) KH, THF, −50 °C to 23 °C, 1.5 h 2) *i*-PrOH, NaOH (3.5 equiv), 85 °C, 5.5 h	ratio **III.63a** : **III.44** = 11.5 : 1 d.r. **III.63a** : **III.63b** = 9 : 1

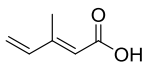
[a] ratios determined by ^{1}H NMR spectroscopy.



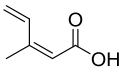
III.45 **III.47**

Procedure B: A Schlenk tube was charged with washed potassium hydride (2.4 equiv) and tetrahydrofuran (1 M). A solution of allyl alcohol (1 equiv) in tetrahydrofuran (0.75 M) was added

at 0 °C. After 35 min, the reaction was cooled to −50 °C, trichloroethene (**III.20**) (1.2 equiv) in tetrahydrofuran (0.8 M) was added and the reaction was allowed to warm to 23 °C. After 1.5 h, *iso*-propanol (0.28 M) and sodium hydroxide (3.5 equiv) were added and the reaction mixture was heated to 85 °C. After 5 h, water and aqueous hydrochloric acid solution (2 M) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×). The combined organic layers were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel. The dr of the substrate was analyzed by ^{1}H NMR spectroscopy.



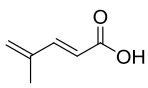
III.66a



III.66b

Following the general procedure, crotyl alcohol (**III.51**) (48.6 mg, 0.674 mmol) provided a mixture of dienes **III.66a** and **III.66b** (40.0 mg, 53%, d.r. = 1 : 0.77) as a brown solid without purification.

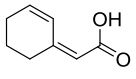
The obtained analytical data were in full agreement with those reported in the literature.[208]



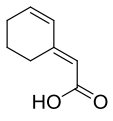
III.64

Following the general procedure, 2-methyl-2-propen-1-ol (**III.52**) (71.7 mg, 0.994 mmol) provided diene **III.64** (110 mg, 99%) as a brown solid without purification.

The obtained analytical data were in full agreement with those reported in the literature.[206]



III.68a



III.68b

Following the general procedure, 2-cyclohexenol (**III.67**) (55.6 mg, 0.566 mmol) provided a mixture of dienes **III.68a** and **III.68b** (24.0 mg, 31%, d.r. = 1:1) as a white solid after flash column chromatography on silica gel (9% ethyl acetate and 1% acetic acid in hexanes).

Analytical data for III.68a and III.68b:

*Note: Asterisks denote the signals of the E-isomer **III.68b**, but not all signals could be assigned.*

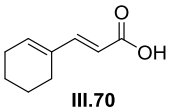
TLC (20% diethyl ether in hexanes), R_f = 0.26 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.43 (s, 2H), 7.46 (d, *J* = 10.2 Hz, 1H), 6.28 (dq, *J* = 8.9, 4.1 Hz, 2H), 6.14 (d, *J* = 9.8 Hz, 1H)*, 5.59 (s, 1H)*, 5.50 (s, 1H), 3.01 – 2.92 (m, 2H)*, 2.47 – 2.36 (m, 2H), 2.22 (dd, *J* = 13.9, 6.0 Hz, 4H), 1.76 (dp, *J* = 25.6, 6.1 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.0*, 172.3, 156.6*, 155.3, 139.5, 139.2*, 130.3*, 125.3, 114.5*, 112.5, 32.9, 26.6*, 26.3, 25.7*, 22.7, 21.9*.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2923 (*m*), 1681 (*s*), 1614 (*s*), 1587 (*s*), 1420 (*m*), 1391 (*w*), 1338 (*w*), 1258 (*s*), 1242 (*s*), 1187 (*s*), 1131 (*m*), 1049 (*m*), 918 (*s*), 871 (*vs*), 691 (*s*) cm^{-1}.

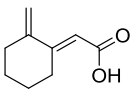
HRMS (EI) calcd for $C_8H_{10}O_2$ $[M]^+$: 138.0675; found: 138.0681.



III.70

Following the general procedure, 2-methylenecyclohexan-1-ol (**III.69**) (104 mg, 0.931 mmol) provided the diene **III.70** (6.00 mg, 4%) as a beige solid after flash column chromatography on silica gel (17% to 50% ethyl acetate in hexanes).

The obtained analytical data were in full agreement with those reported in the literature.[209]



III.72

Following the general procedure, cyclohex-1-en-1-ylmethanol (**III.71**) (57.1 mg, 0.509 mmol) provided the diene **III.72** after flash column chromatography on silica gel (9% to 50% ethyl acetate in hexanes).

Analytical data for III.72:

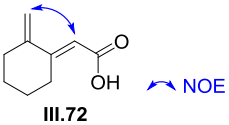
TLC (17% diethyl ether in hexanes), R_f = 0.30 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.28 (s, 1H), 5.86 (s, 1H), 5.02 (s, 1H), 4.80 (s, 1H), 2.93 (t, *J* = 4.9 Hz, 2H), 2.34 (t, *J* = 4.6 Hz, 2H), 1.69 (dt, *J* = 6.7, 3.1 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.2, 164.0, 149.6, 112.4, 111.6, 35.5, 30.1, 26.5, 26.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2933 (*m*), 2859 (*m*), 1682 (*vs*), 1632 (*s*), 1440 (*w*), 1411 (*w*), 1295 (*m*), 1226 (*s*), 1163 (*w*), 902 (*m*), 882 (*w*), 689 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_9H_{12}O_2$ $[M]^+$: 152.0832; found: 152.0829.



III.72

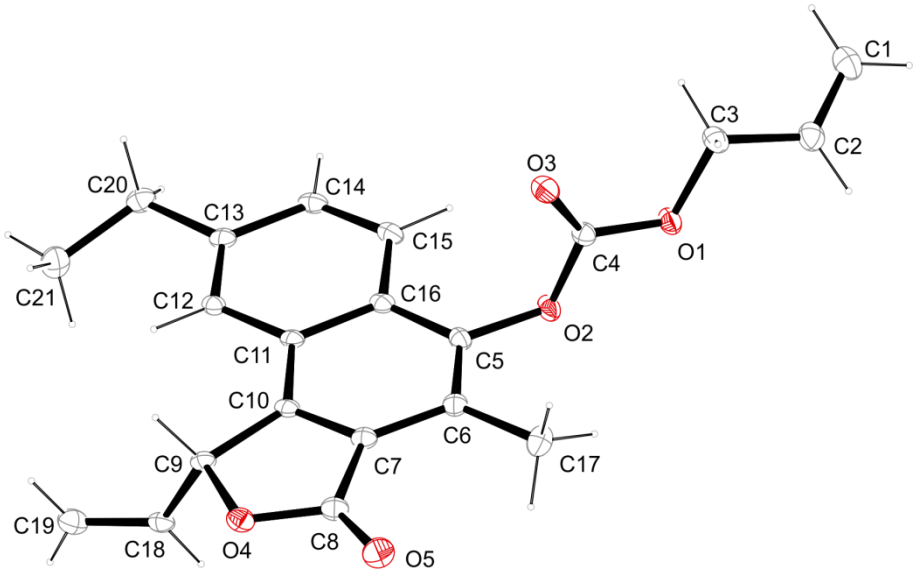
The relative stereochemistry was assigned by NOE correlations.

11 Appendix

11.1 X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR9711 and refined by least-squares methods against *F*2 with SHELXL-97.12 All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

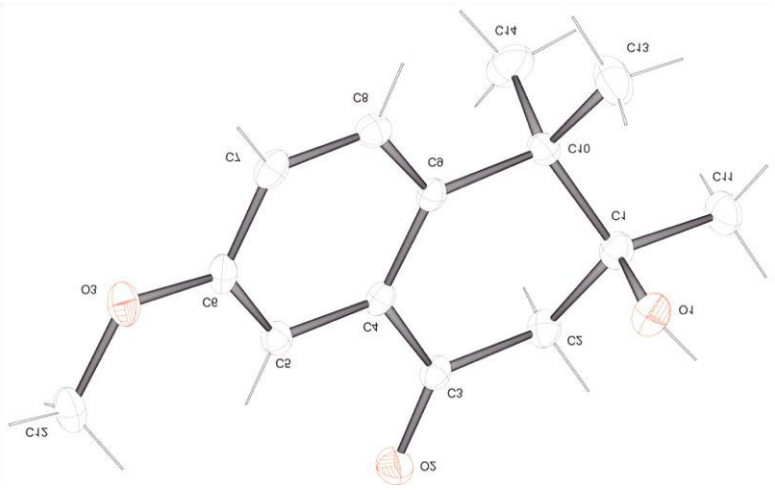
Single-crystal X-ray analysis of compound I.107:



net formula	$C_{21}H_{20}O_5$
M_r/g mol^{-1}	352.37
crystal size/mm	0.100 × 0.090 × 0.010
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	monoclinic
space group	'C 2/c'
a/Å	30.2456(18)
b/Å	7.6603(4)
c/Å	18.2737(11)
α/°	90
β/°	122.731(2)

γ/°	90
V/Å^3	3561.6(4)
Z	8
calc. density/g cm^{-3}	1.314
μ/mm^{-1}	0.094
absorption correction	multi-scan
transmission factor range	0.8940–0.9580
refls. measured	18840
R_{int}	0.0480
mean σ(I)/I	0.0356
θ range	3.202–25.38
observed refls.	2358
x, y (weighting scheme)	0.0393, 2.6371
hydrogen refinement	constr
refls in refinement	3250
parameters	237
restraints	0
$R(F_{obs})$	0.0402
$R_w(F^2)$	0.0956
S	1.058
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.223
min electron density/e Å^{-3}	−0.210

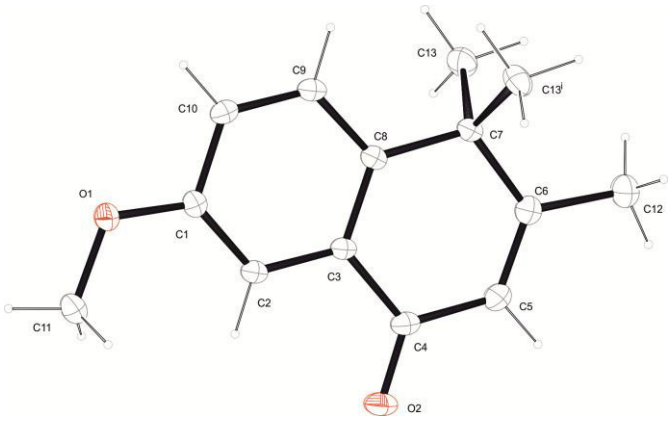
Single-crystal X-ray analysis of compound I.165:



net formula	$C_{14}H_{18}O_3$
M_r/g mol^{-1}	234.28
crystal size/mm	0.090 × 0.040 × 0.030
T/K	100.(2)
radiation	MoKα

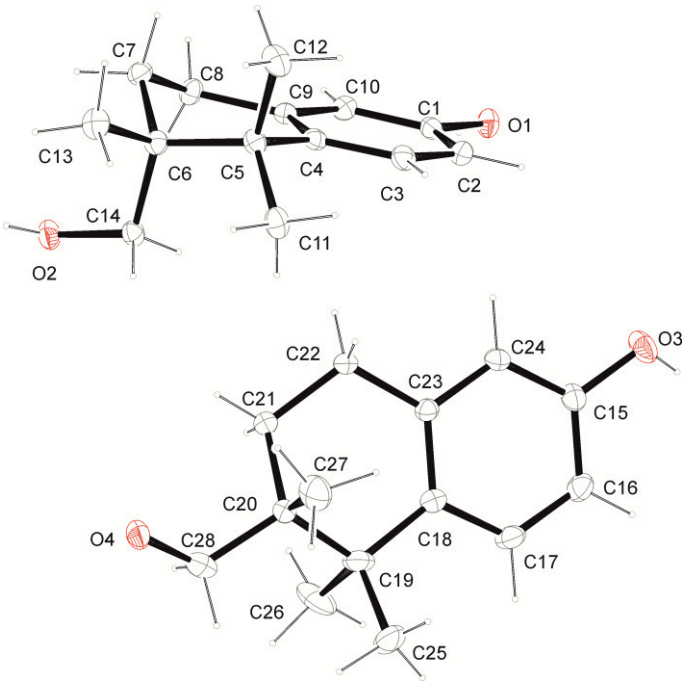
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	7.0271(3)
b/Å	17.0529(7)
c/Å	10.0184(4)
α/°	90
β/°	91.650(2)
γ/°	90
V/Å^3	1200.03(9)
Z	4
calc. density/g cm^{-3}	1.297
μ/mm^{-1}	0.090
absorption correction	Multi-Scan
transmission factor range	0.9017–0.9705
refls. measured	18124
R_{int}	0.0421
mean σ(I)/I	0.0268
θ range	3.137–26.365
observed refls.	2013
x, y (weighting scheme)	0.0528, 1.1304
hydrogen refinement	H(C) constr, H(O) restr
refls in refinement	2450
parameters	162
restraints	1
$R(F_{obs})$	0.0561
$R_w(F^2)$	0.1404
S	1.116
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.496
min electron density/e Å^{-3}	−0.358

Single-crystal X-ray analysis of compound I.166:



net formula	$C_{14}H_{16}O_2$
M_r/g mol^{-1}	216.27
crystal size/mm	0.090 × 0.070 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P n m a'
a/Å	15.3960(5)
b/Å	7.0864(2)
c/Å	10.4521(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	1140.35(6)
Z	4
calc. density/g cm^{-3}	1.260
μ/mm^{-1}	0.083
absorption correction	Multi-Scan
transmission factor range	0.9123–0.9705
refls. measured	12854
R_{int}	0.0310
mean σ(I)/I	0.0191
θ range	3.287–28.272
observed refls.	1332
x, y (weighting scheme)	0.0630, 0.3244
hydrogen refinement	constr
refls in refinement	1533
parameters	97
restraints	0
$R(F_{obs})$	0.0394
$R_w(F^2)$	0.1145
S	1.065
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.402
min electron density/e Å^{-3}	−0.210

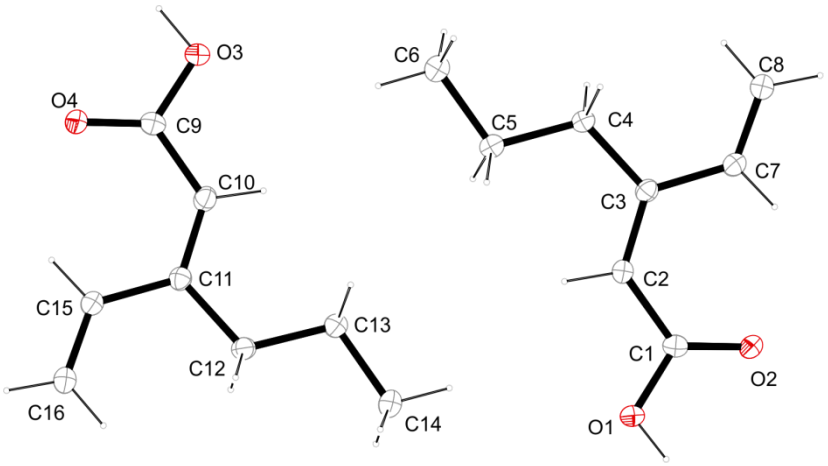
Single-crystal X-ray analysis of compound I.241:



net formula	$C_{14}H_{20}O_2$
M_r/g mol^{-1}	220.30
crystal size/mm	0.070 × 0.060 × 0.030
T/K	103.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	13.2972(7)
b/Å	11.6884(6)
c/Å	15.5919(8)
α/°	90
β/°	99.159(2)
γ/°	90
V/Å^3	2392.4(2)
Z	8
calc. density/g cm^{-3}	1.223
μ/mm^{-1}	0.080
absorption correction	Multi-Scan
transmission factor range	0.9360–0.9705
refls. measured	17874
R_{int}	0.0507
mean σ(I)/I	0.0434
θ range	3.169–25.350
observed refls.	3246
x, y (weighting scheme)	0.0440, 1.2903
hydrogen refinement	mixed

refls in refinement	4368
parameters	371
restraints	27
$R(F_{obs})$	0.0493
$R_w(F^2)$	0.1200
S	1.032
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.241
min electron density/e Å^{-3}	−0.239

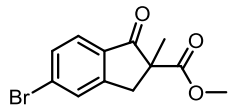
Single-crystal X-ray analysis of compound III.62b:

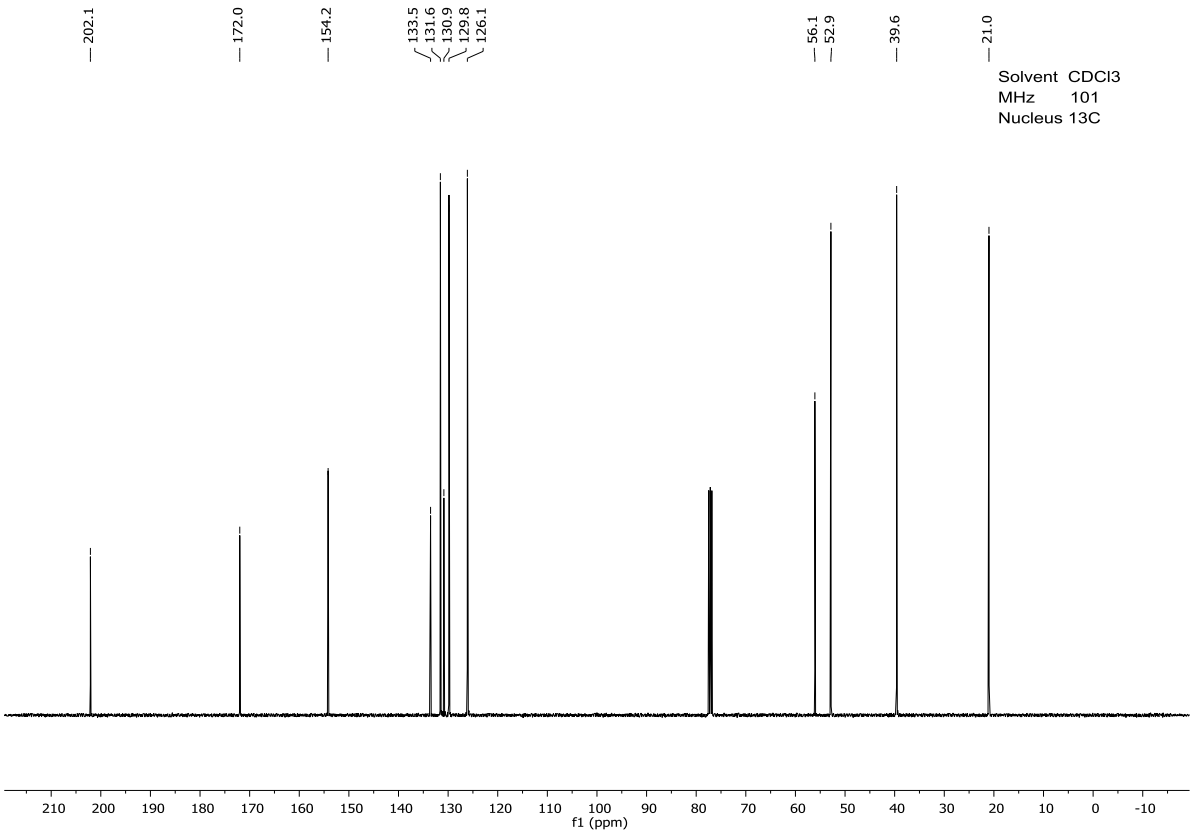


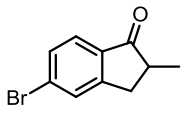
net formula	$C_8H_{12}O_2$
M_r/g mol^{-1}	140.180
crystal size/mm	0.254 × 0.112 × 0.059
T/K	123(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	7.4344(7)
b/Å	9.1982(7)
c/Å	12.4795(13)
α/°	81.541(7)
β/°	81.300(8)
γ/°	68.583(8)
V/Å^3	781.39(12)
Z	4
calc. density/g cm^{-3}	1.19161(18)
μ/mm^{-1}	0.084
absorption correction	'multi-scan'

transmission factor range	0.90603–1.00000
refls. measured	3969
R_{int}	0.0224
mean $\sigma(I)/I$	0.0669
θ range	4.21–25.34
observed refls.	1881
x, y (weighting scheme)	0.0459, 0.0586
hydrogen refinement	mixed
refls in refinement	2817
parameters	191
restraints	0
$R(F_{obs})$	0.0537
$R_w(F^2)$	0.1267
S	1.025
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.193
min electron density/e Å^{-3}	−0.228

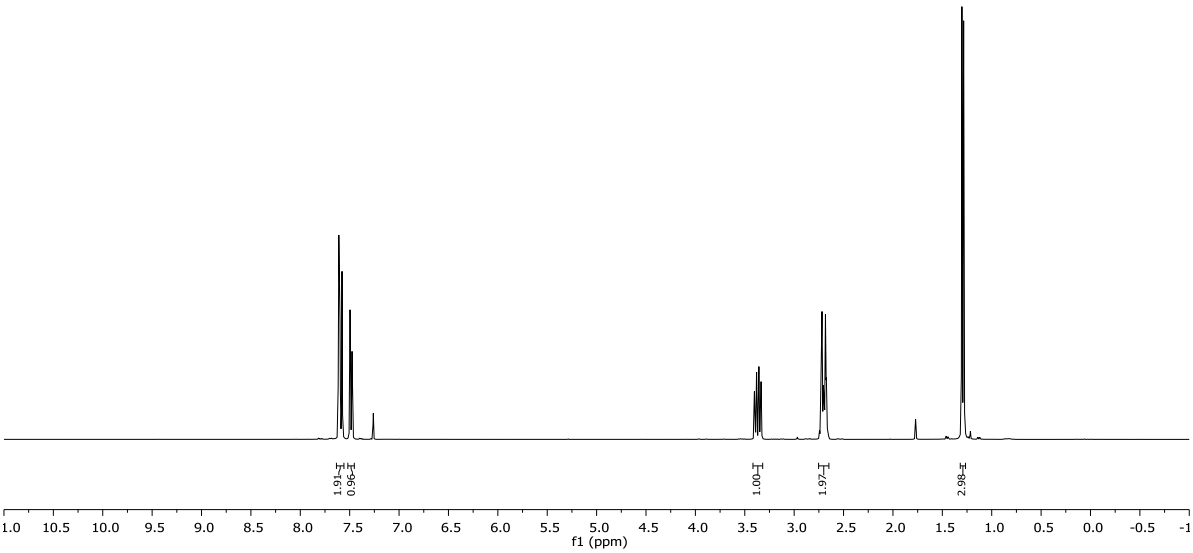
11.2 NMR Spectra of Chapter I





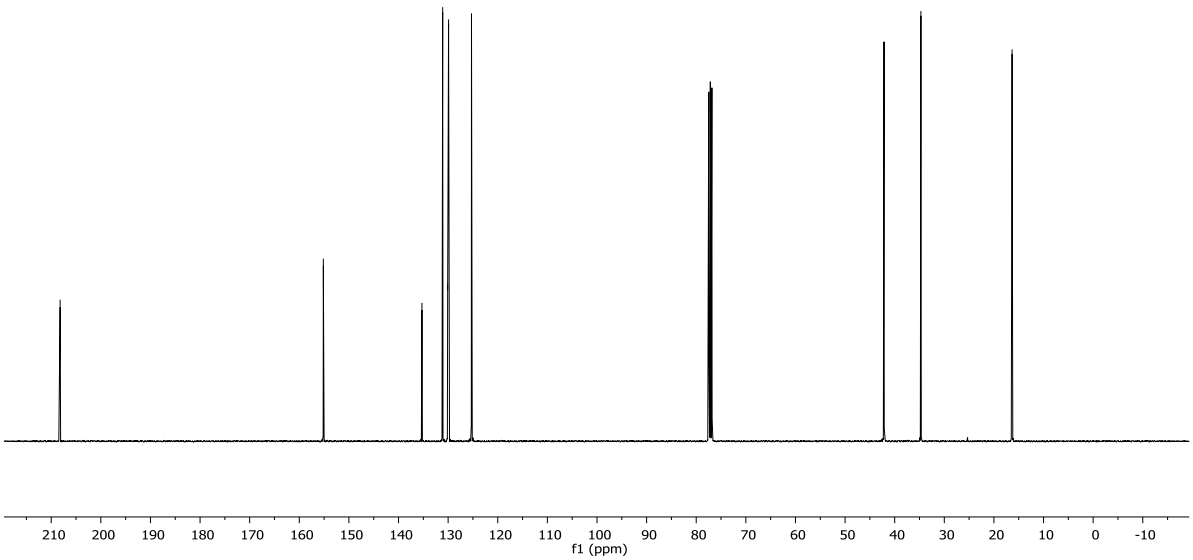


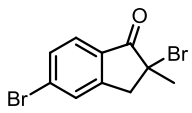
Solvent CDCl3
MHz 400
Nucleus 1H



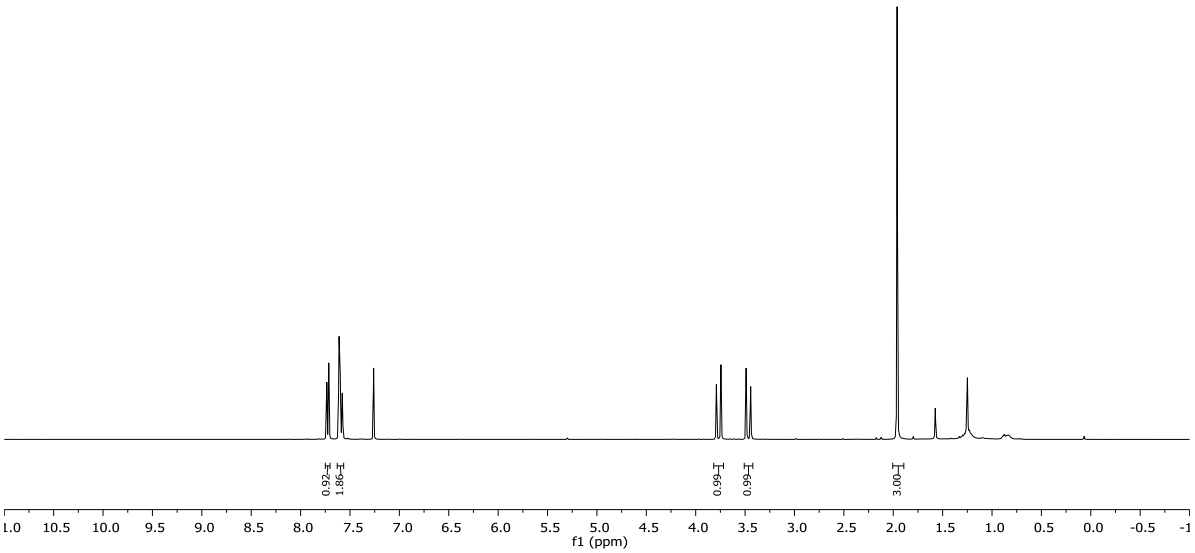
208.2
155.2
135.3
131.1
130.1
129.9
125.3
42.1
34.7
16.3

Solvent CDCl3
MHz 101
Nucleus 13C

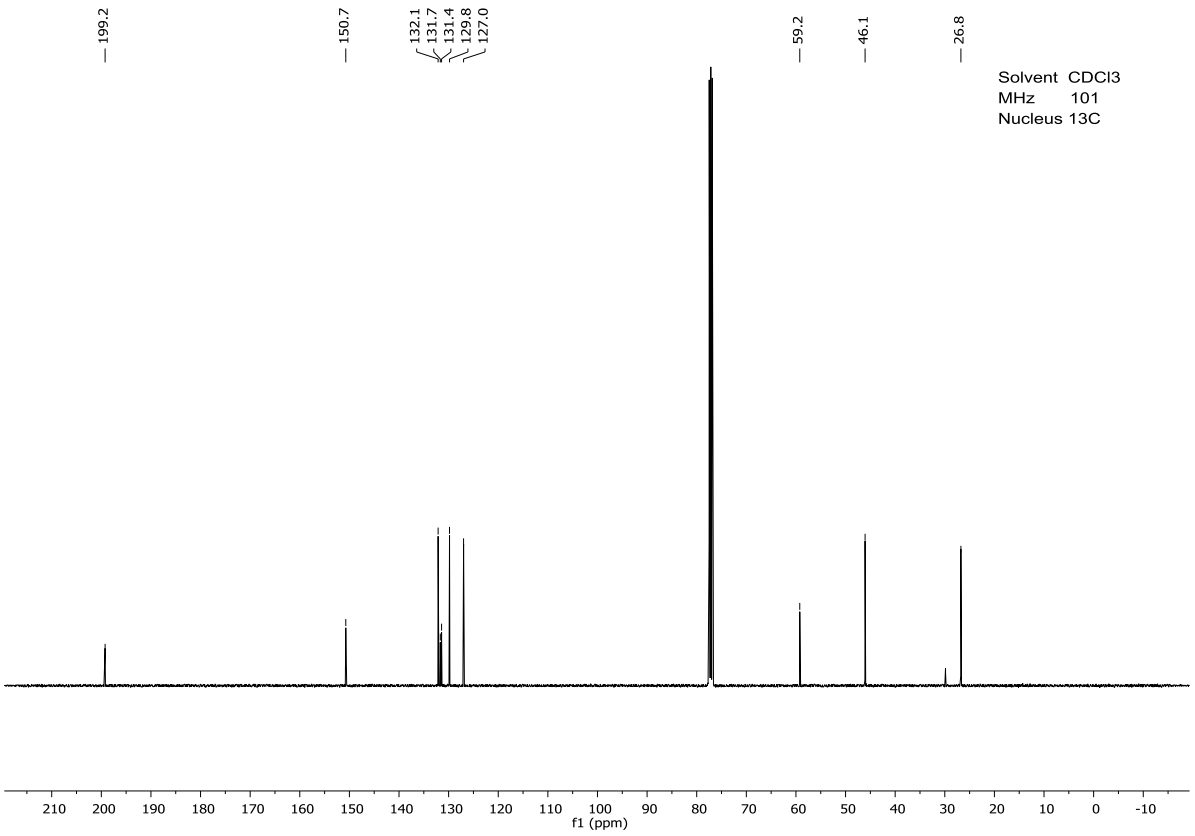


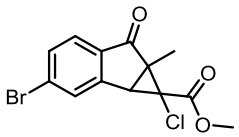


Solvent CDCl3
MHz 400
Nucleus 1H

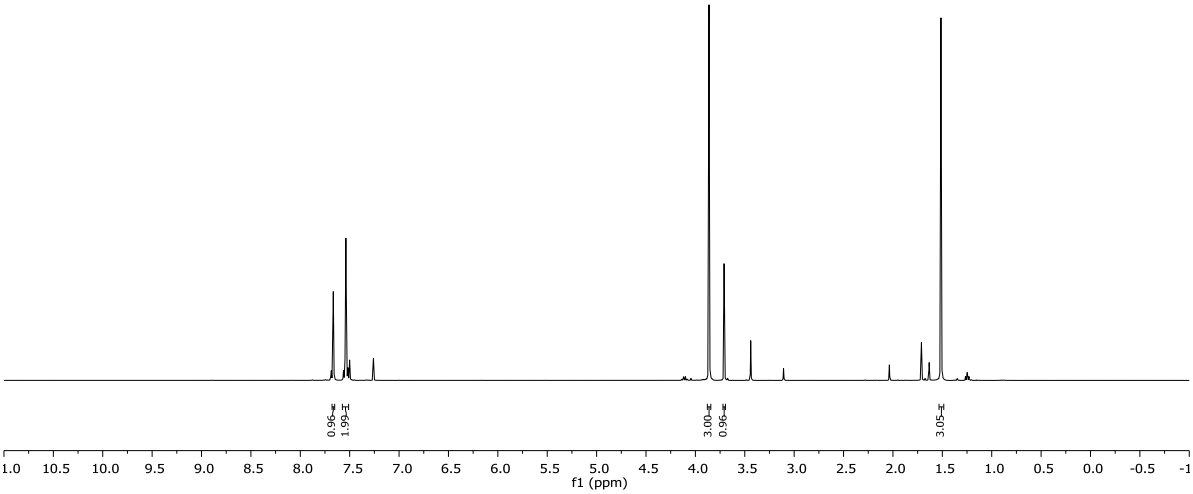


Solvent CDCl3
MHz 101
Nucleus 13C



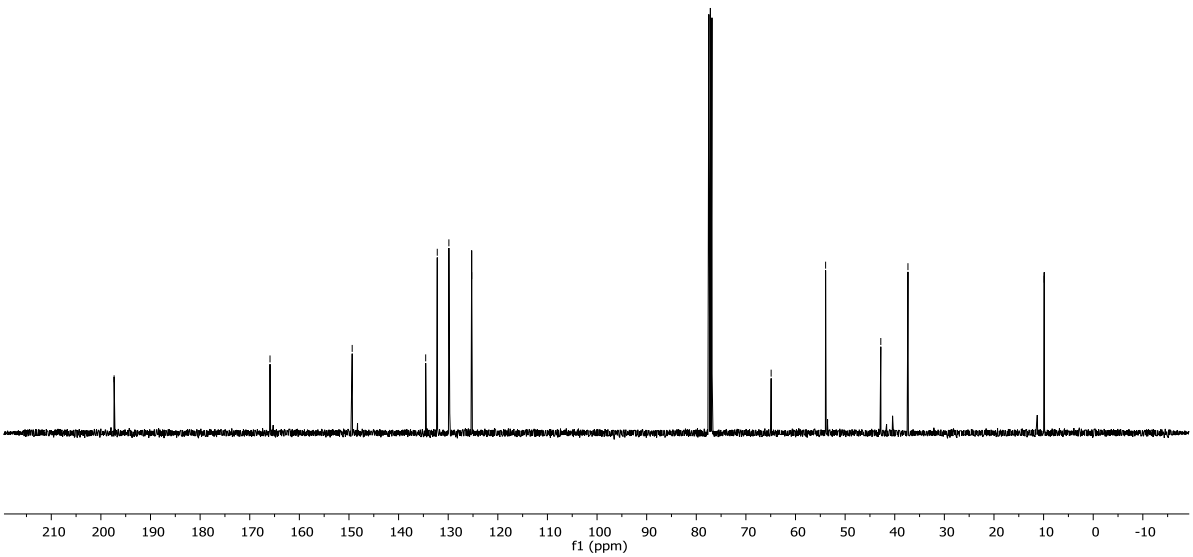


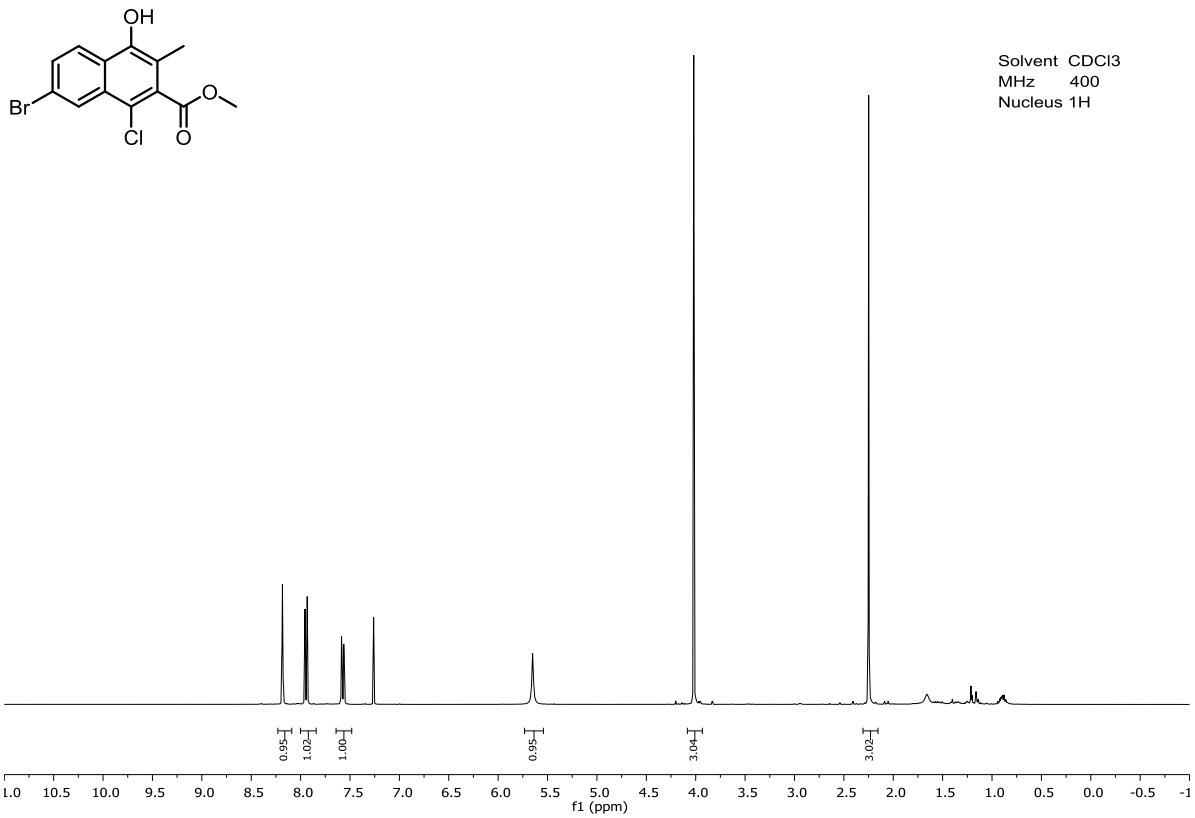
Solvent CDCl3
MHz 400
Nucleus 1H

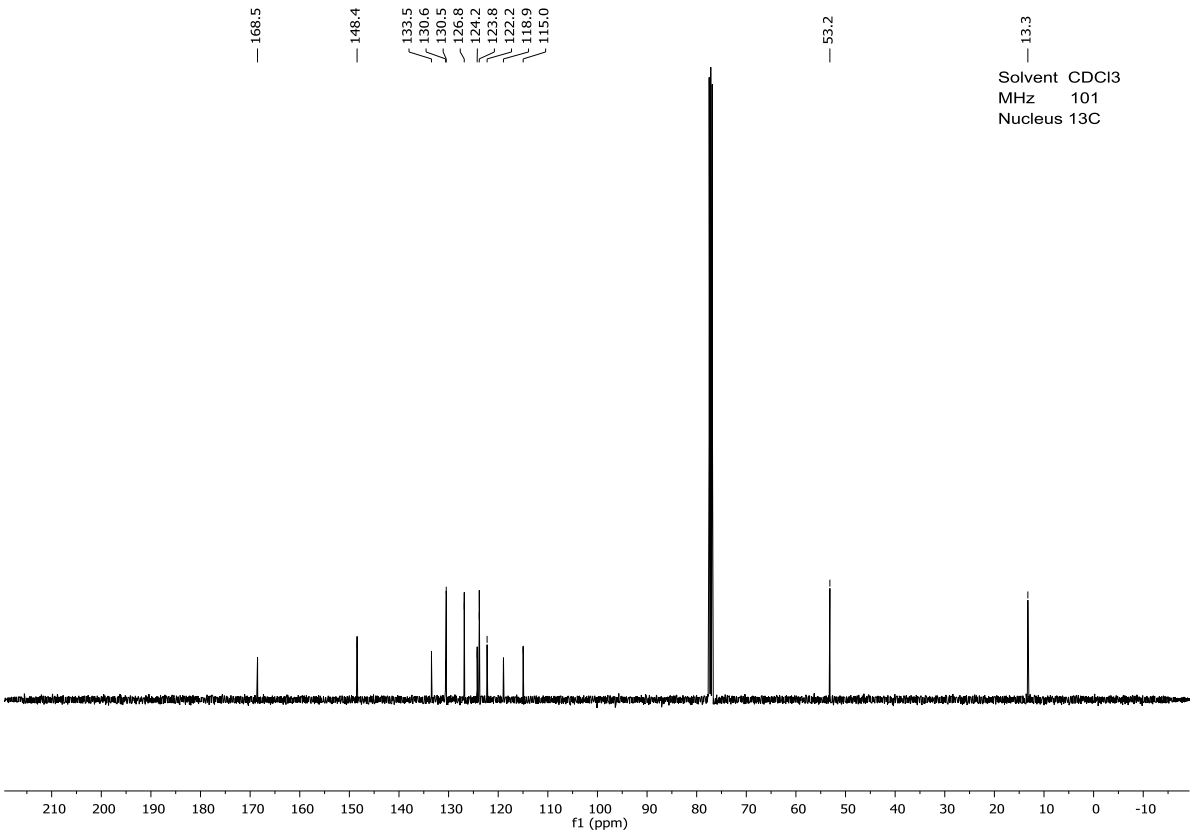


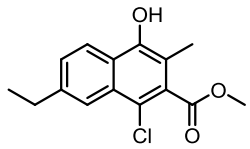
197.3
165.9
149.4
134.5
132.2
129.9
129.8
125.3
64.9
53.9
42.8
37.3
9.9

Solvent CDCl3
MHz 101
Nucleus 13C

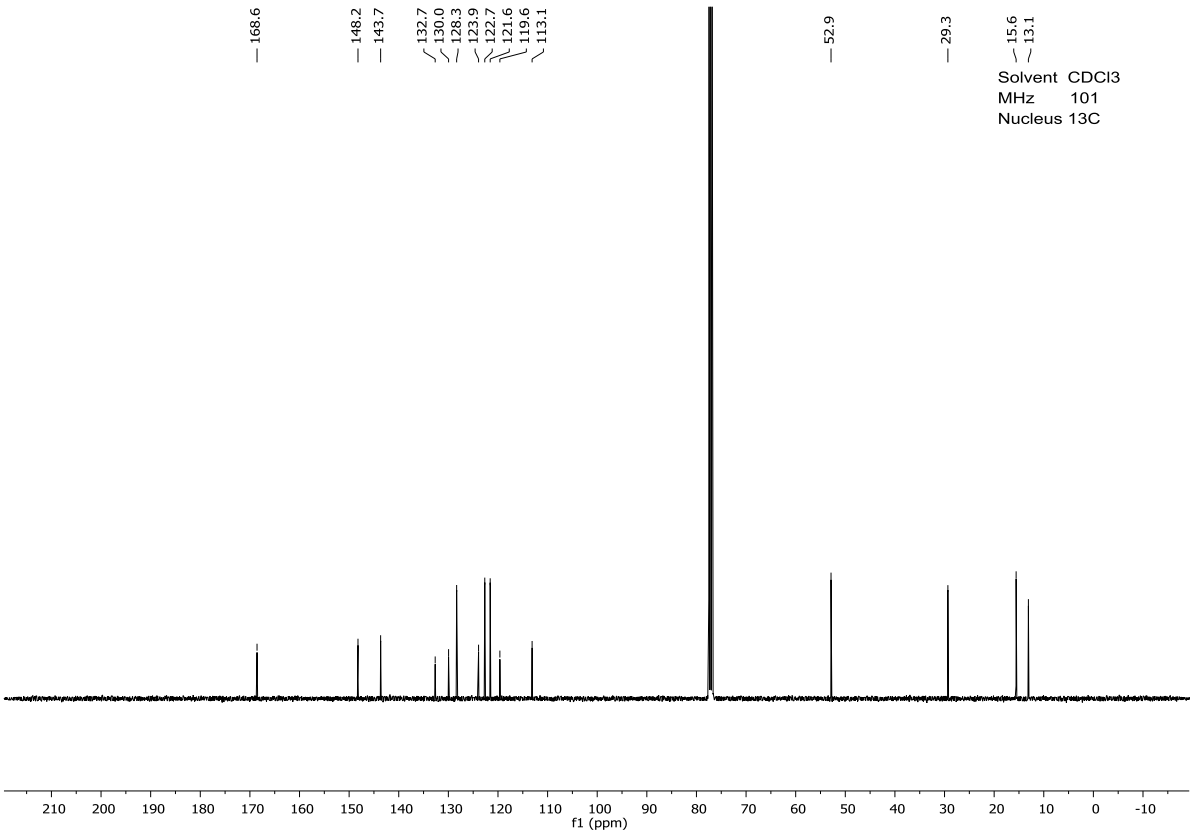


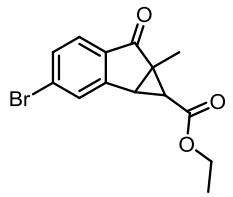

OH
Br
Cl
O
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.95
1.02
1.00
0.95
3.04
3.02
f1 (ppm)


168.5
148.4
133.5
130.6
130.5
126.8
124.2
123.8
122.2
118.9
115.0
53.2
13.3
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

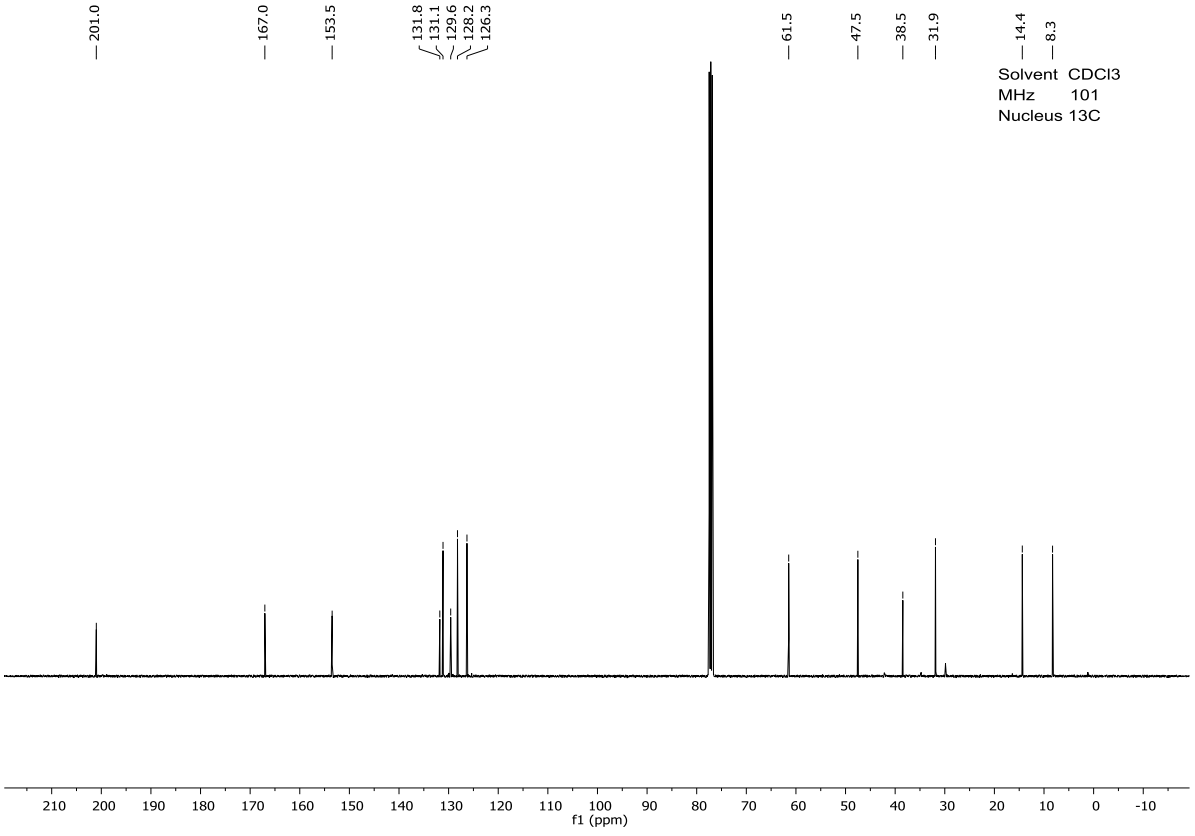

OH
O
Cl
O

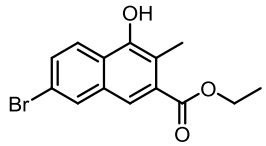
Solvent CDCl3
MHz 400
Nucleus 1H
1.02
0.99
1.01
1.00
3.00
2.08
3.03
3.09
f1 (ppm)


168.6
148.2
143.7
132.7
130.0
128.3
123.9
122.7
121.6
119.6
113.1
52.9
29.3
15.6
13.1
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

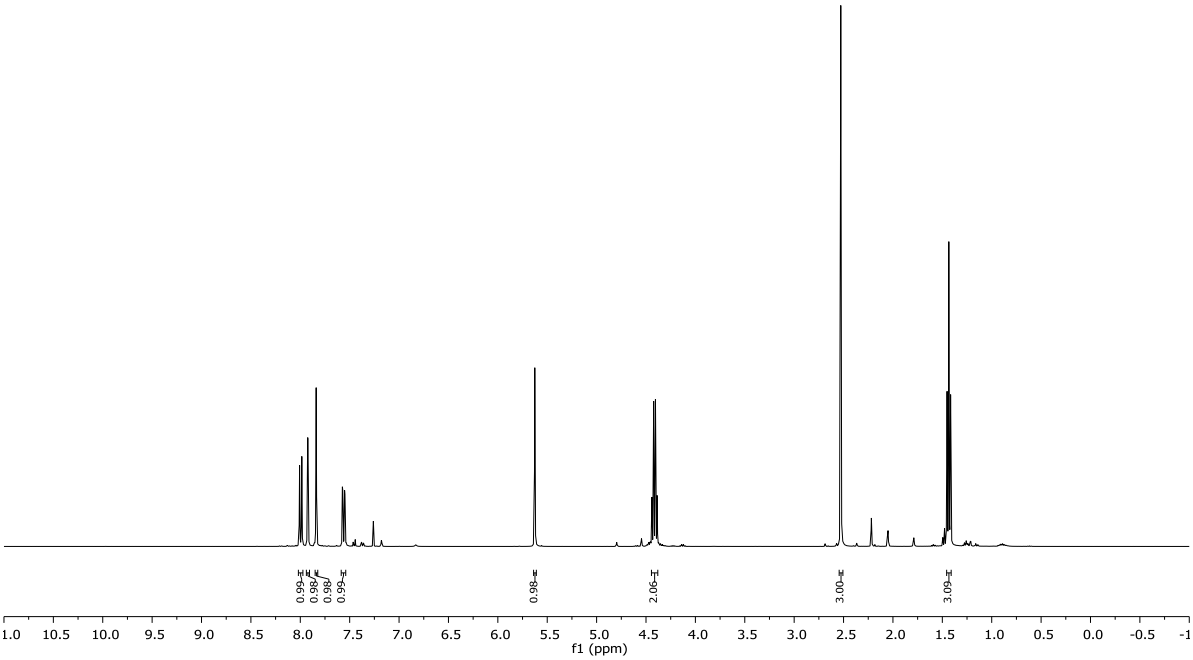

O
Br
O
O

Solvent CDCl3
MHz 400
Nucleus 1H
0.93
1.00
0.98
2.00
0.97
0.94
2.96
3.55
f1 (ppm)


201.0
167.0
153.5
131.8
131.1
129.6
128.2
126.3
61.5
47.5
38.5
31.9
14.4
8.3
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

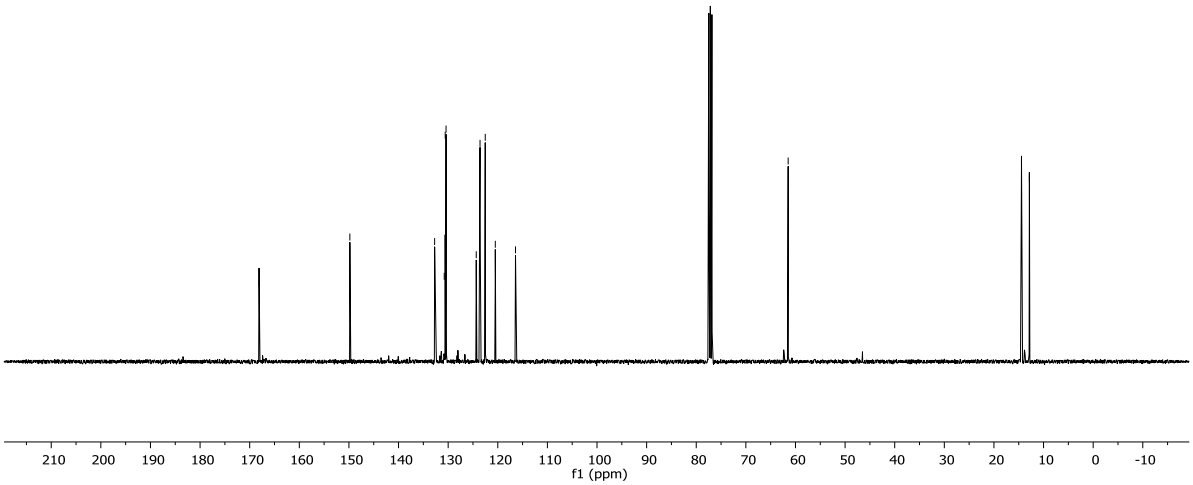


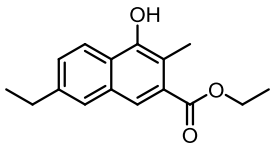
Solvent CDCl3
MHz 400
Nucleus 1H



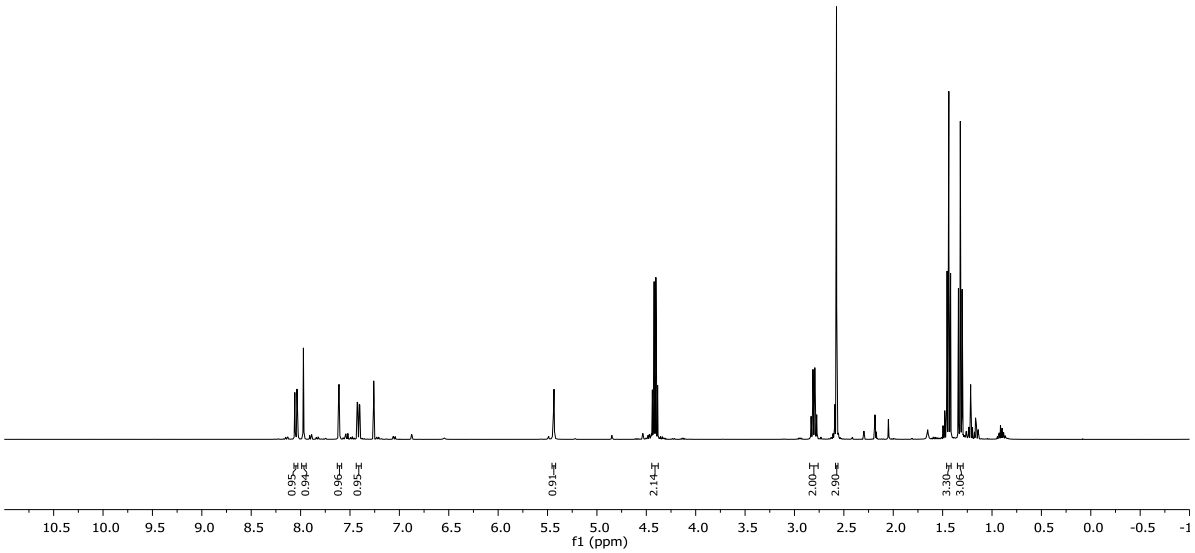
168.1
149.8
132.7
130.8
130.6
130.4
124.3
123.6
122.5
120.5
116.4
61.5
14.5
12.9

Solvent CDCl3
MHz 101
Nucleus 13C



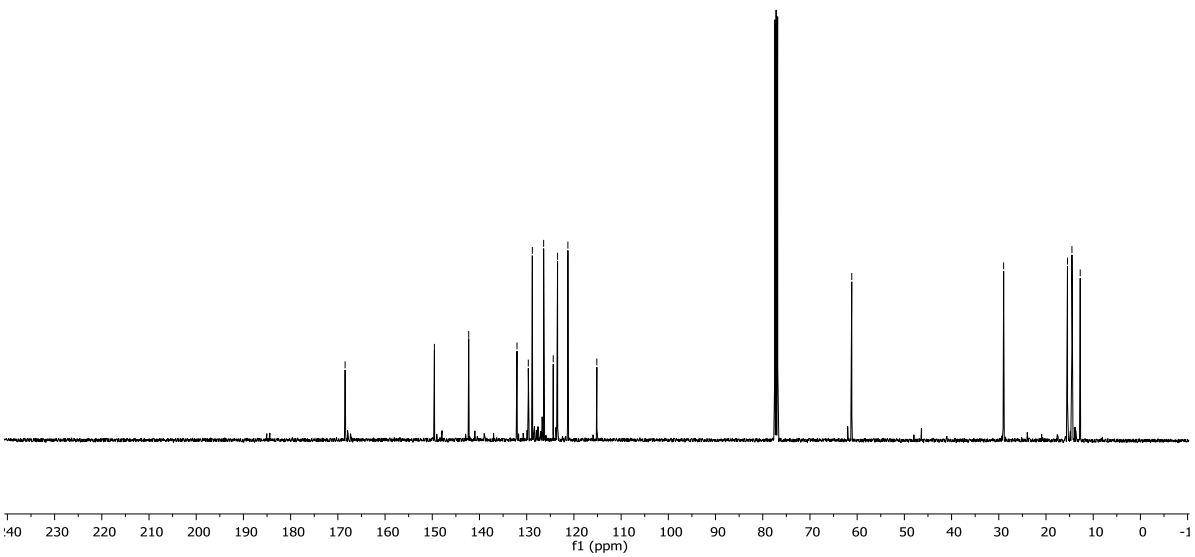


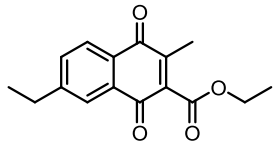
Solvent CDCl3
MHz 400
Nucleus 1H



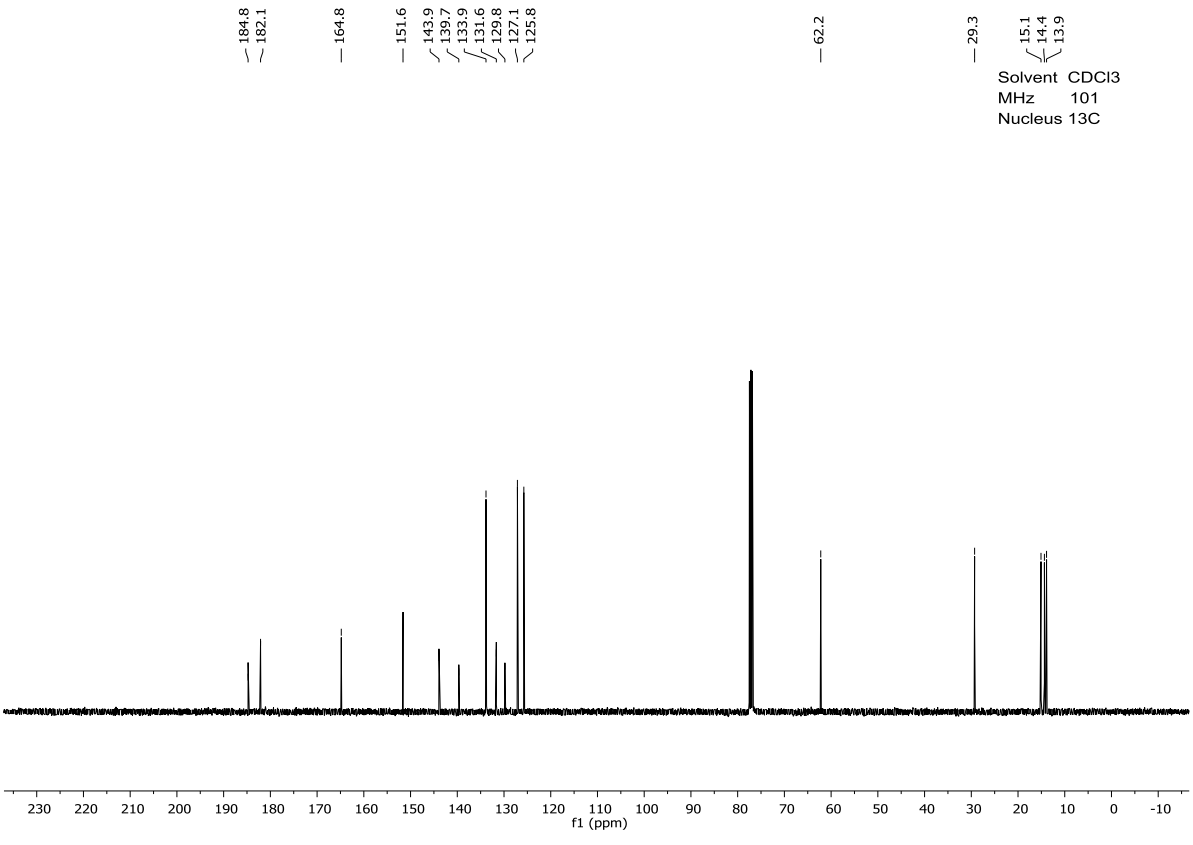
168.5
149.6
142.3
132.1
129.7
128.8
126.4
124.4
123.5
121.3
115.1
61.1
29.0
15.4
14.5
12.7

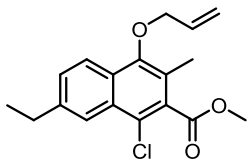
Solvent CDCl3
MHz 101
Nucleus 13C



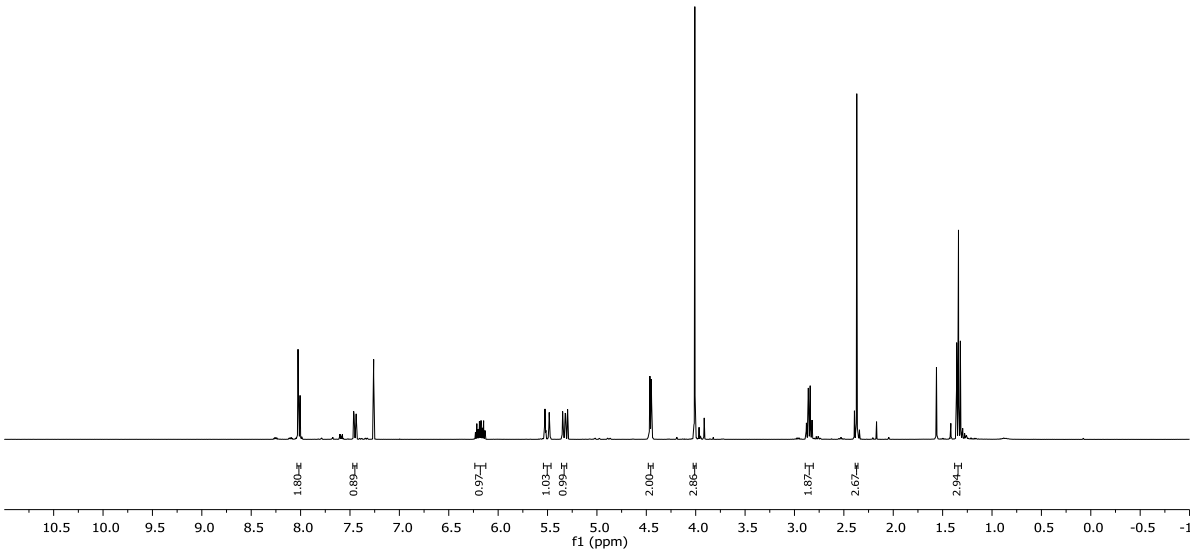


Solvent CDCl3
MHz 400
Nucleus 1H
0.96
0.92
1.07
2.16
2.27
3.00
3.21
3.20
f1 (ppm)


184.8
182.1
164.8
151.6
143.9
139.7
133.9
131.6
129.8
127.1
125.8
62.2
29.3
15.1
14.4
13.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

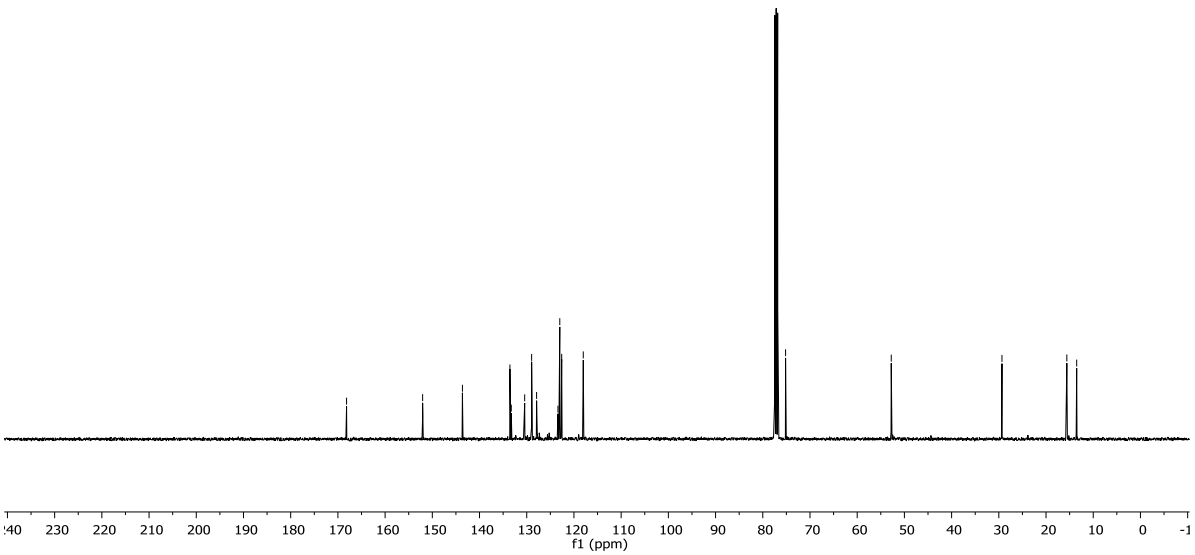


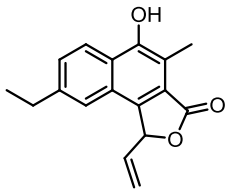
Solvent CDCl3
MHz 400
Nucleus 1H



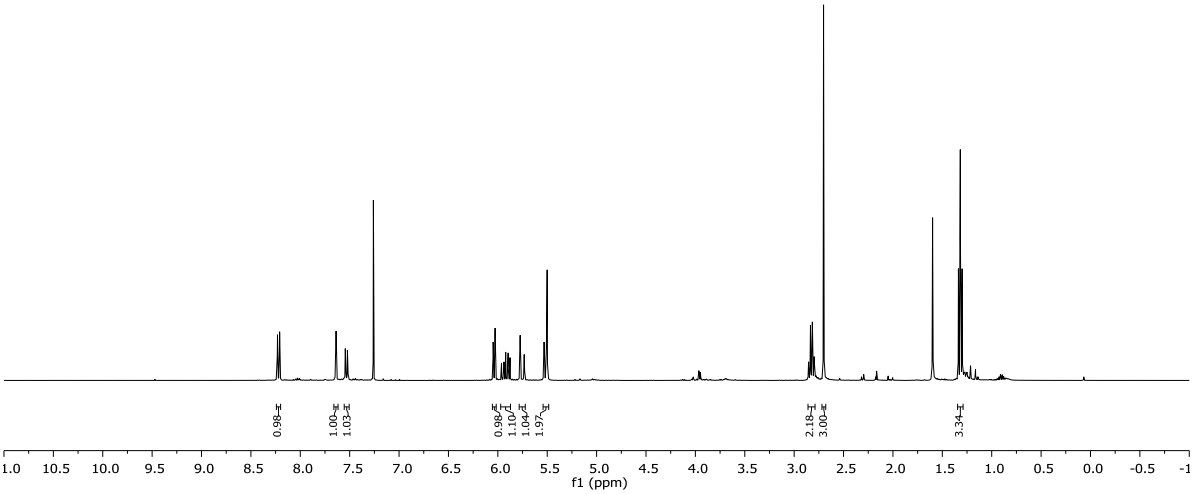
168.2
152.1
143.6
133.6
133.3
130.4
129.0
127.9
123.4
123.0
122.6
118.0
75.2
52.8
29.3
15.6
13.5

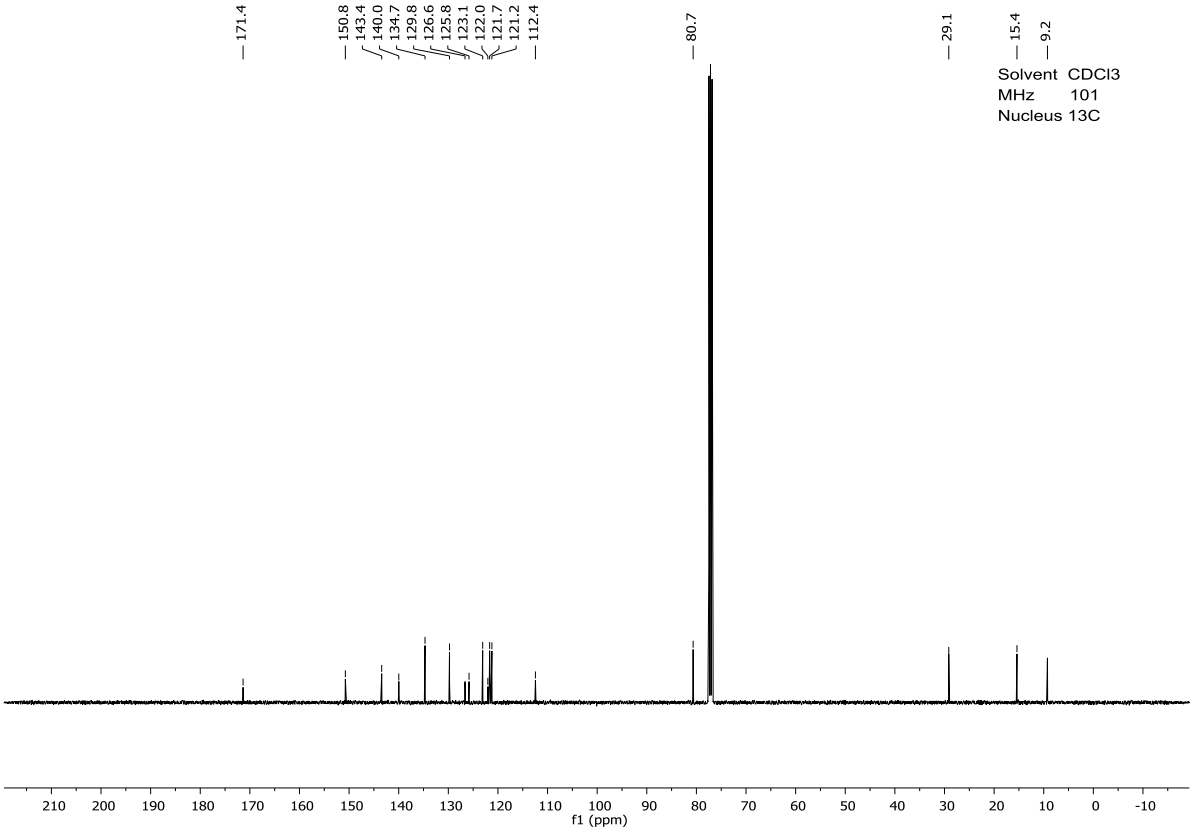
Solvent CDCl3
MHz 101
Nucleus 13C

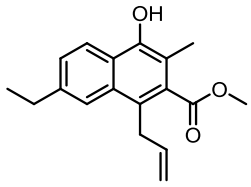




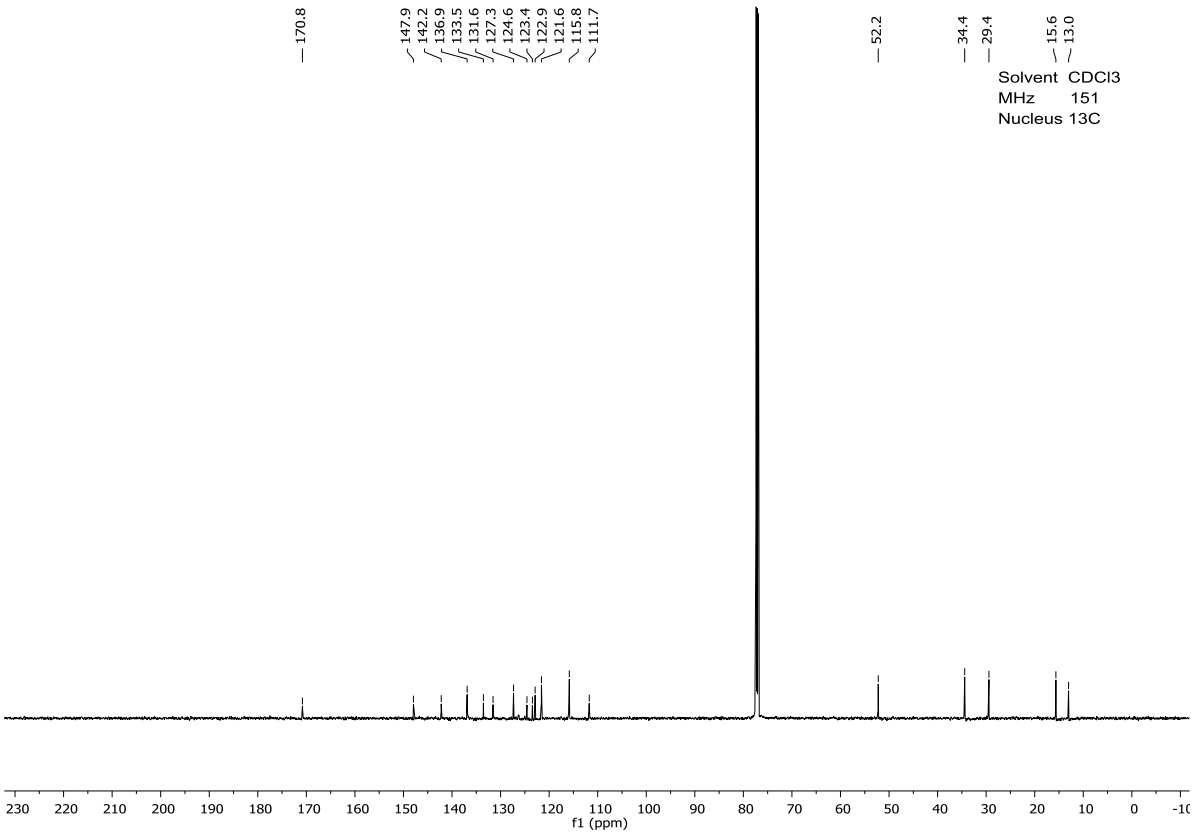
Solvent CDCl3
MHz 400
Nucleus 1H

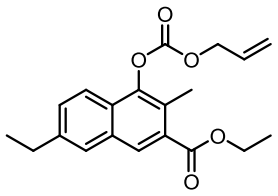


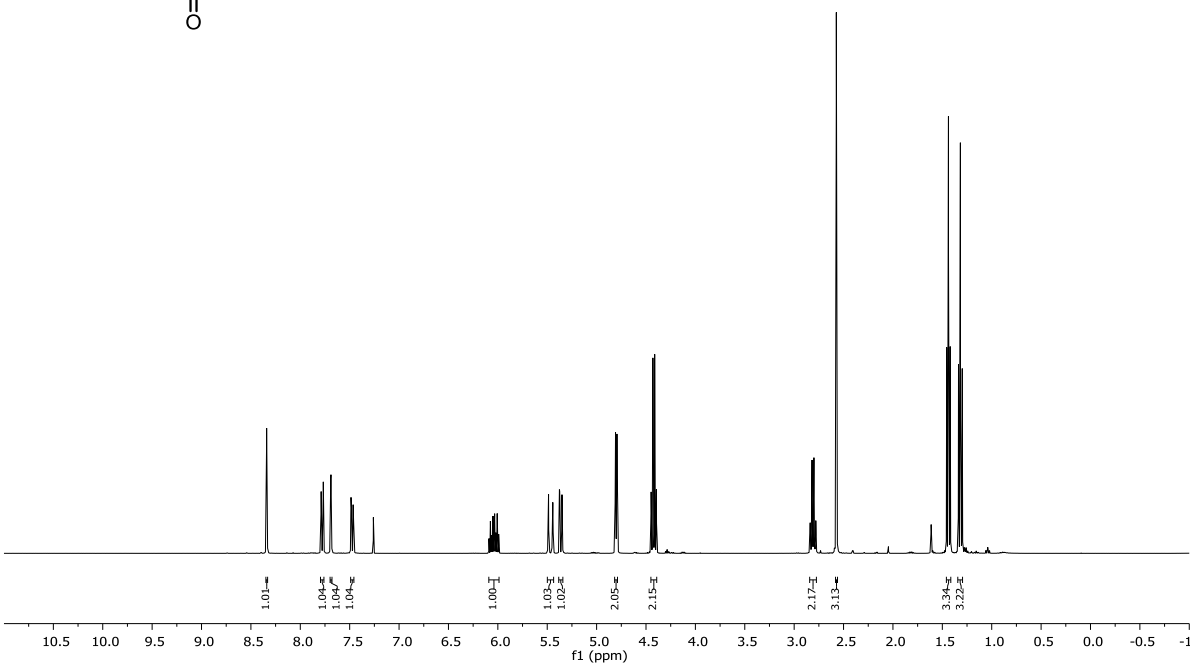


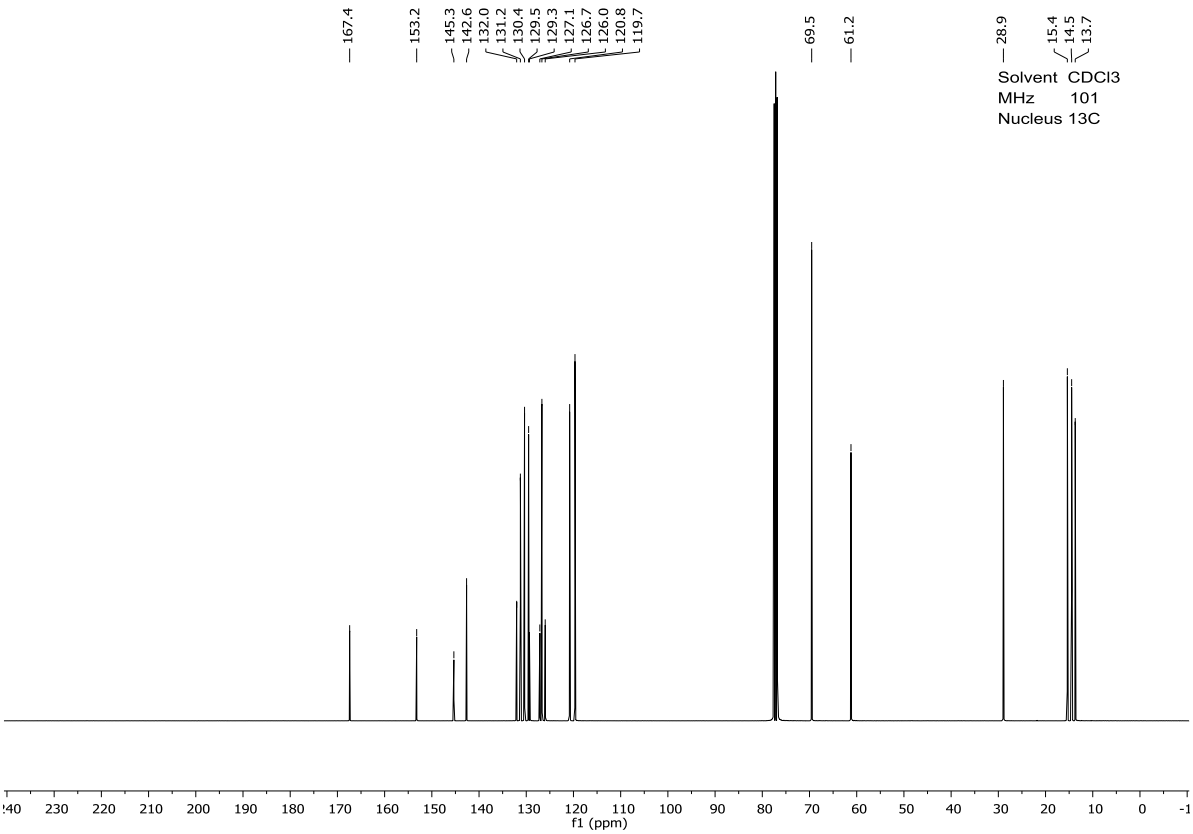

OH
O
O

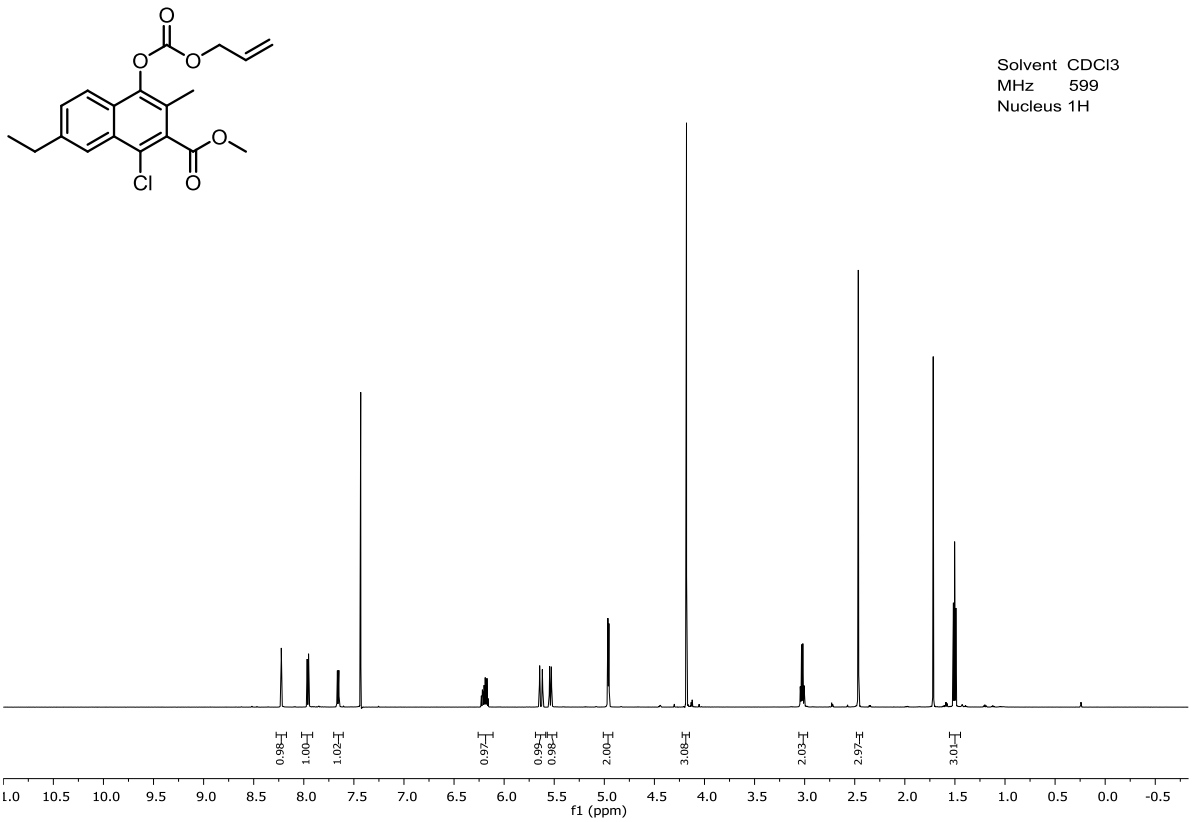
Solvent CDCl3
MHz 599
Nucleus 1H
0.94
0.93
0.90
1.16
0.89
2.07
2.95
2.06
2.01
2.71
2.99
f1 (ppm)

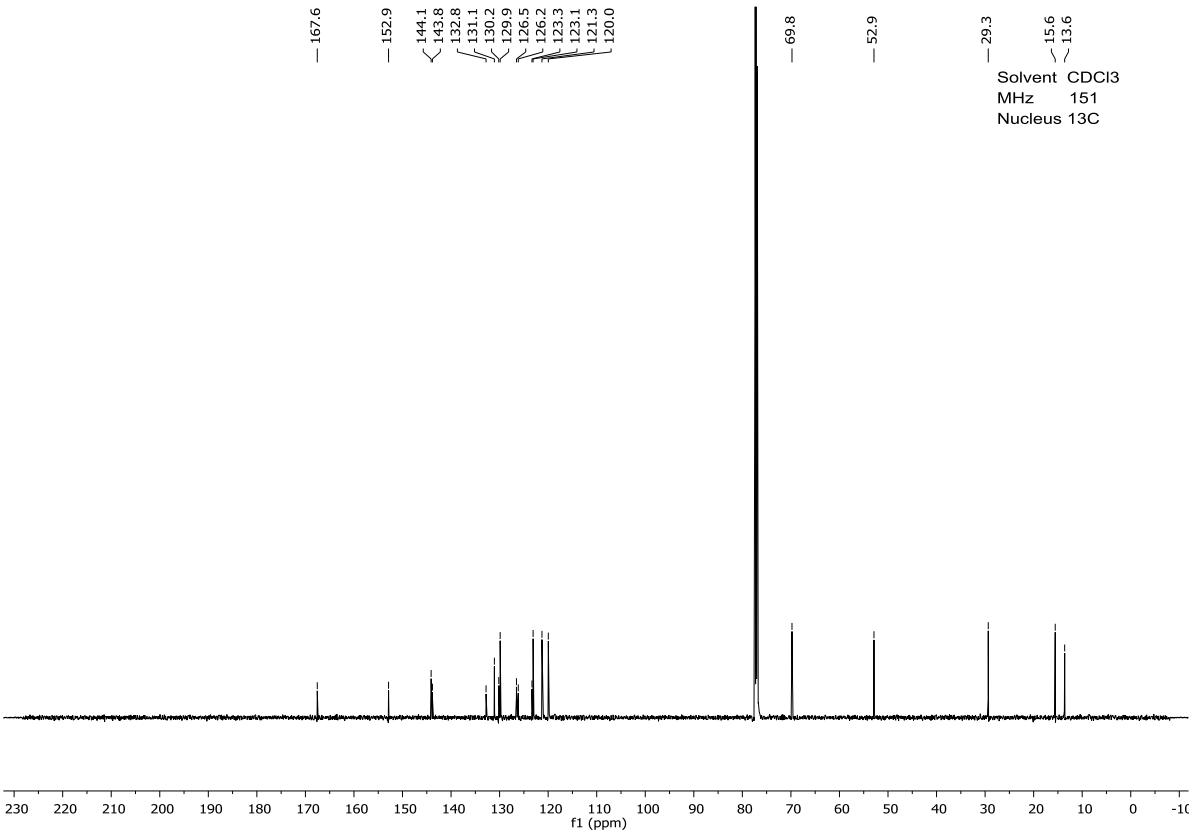

170.8
147.9
142.2
136.9
133.5
131.6
127.3
124.6
123.4
122.9
121.6
115.8
111.7
52.2
34.4
29.4
15.6
13.0
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

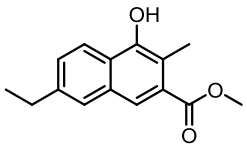



Solvent CDCl3
MHz 400
Nucleus 1H
1.01
1.04
1.04
1.04
1.00
1.03
1.02
2.05
2.15
2.17
3.13
3.34
3.22
f1 (ppm)

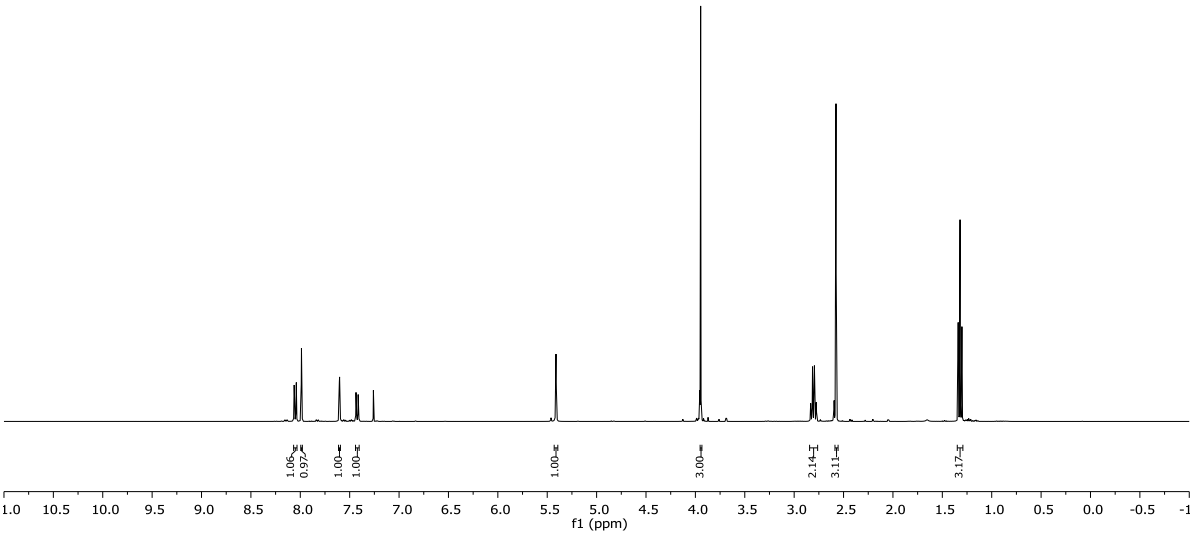

167.4
153.2
145.3
142.6
132.0
131.2
130.4
129.5
129.3
127.1
126.7
126.0
120.8
119.7
69.5
61.2
28.9
15.4
14.5
13.7
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


Solvent CDCl3
MHz 599
Nucleus 1H
0.98
1.00
1.02
0.97
0.99
0.98
2.00
3.08
2.03
2.97
3.01
f1 (ppm)


167.6
152.9
144.1
143.8
132.8
131.1
130.2
129.9
126.5
126.2
123.3
123.1
121.3
120.0
69.8
52.9
29.3
15.6
13.6
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

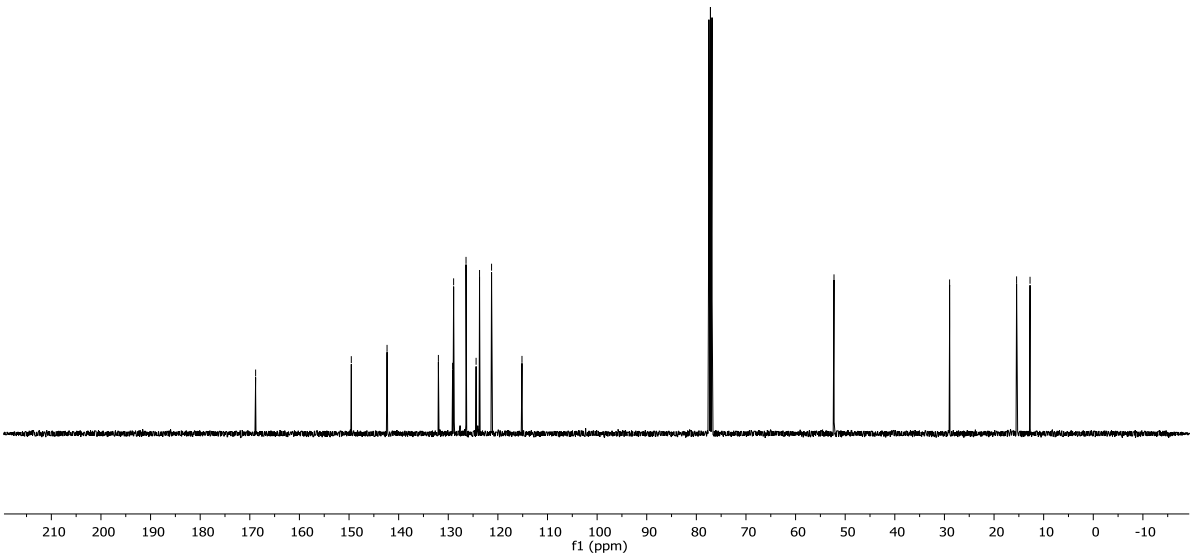


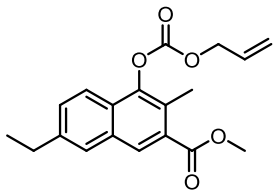
Solvent CDCl3
MHz 400
Nucleus 1H



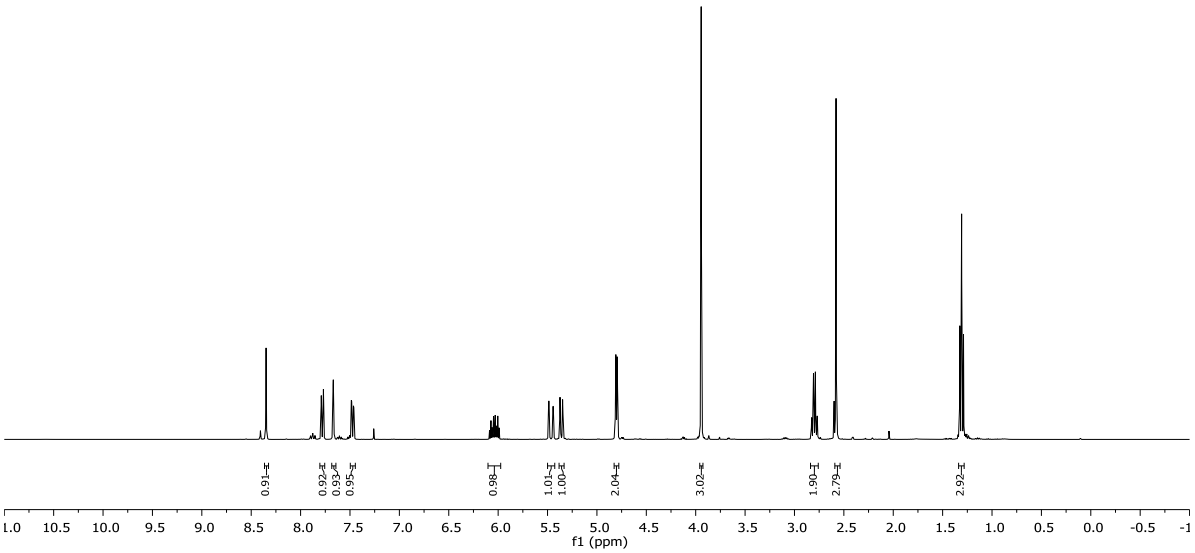
168.8
149.5
142.3
132.0
129.1
128.9
126.4
124.4
123.7
121.3
115.1
52.3
29.0
15.5
12.7

Solvent CDCl3
MHz 101
Nucleus 13C



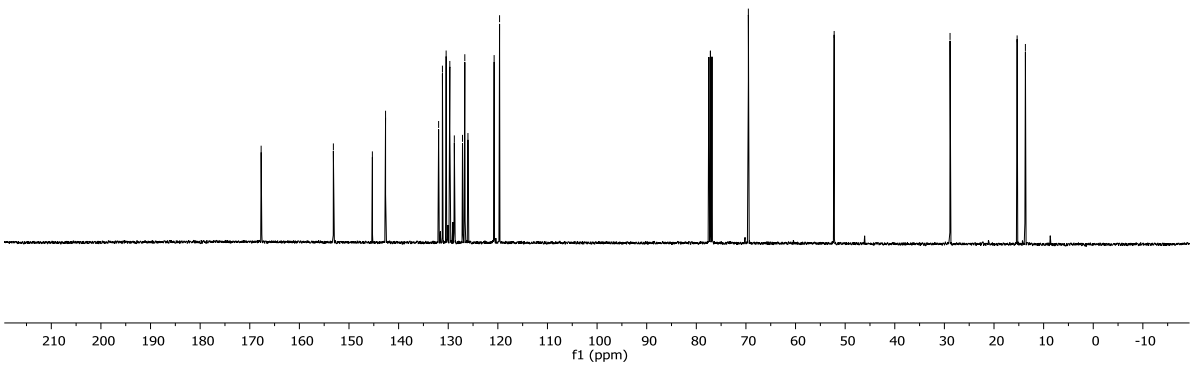


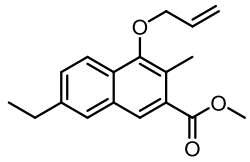
Solvent CDCl3
MHz 400
Nucleus 1H



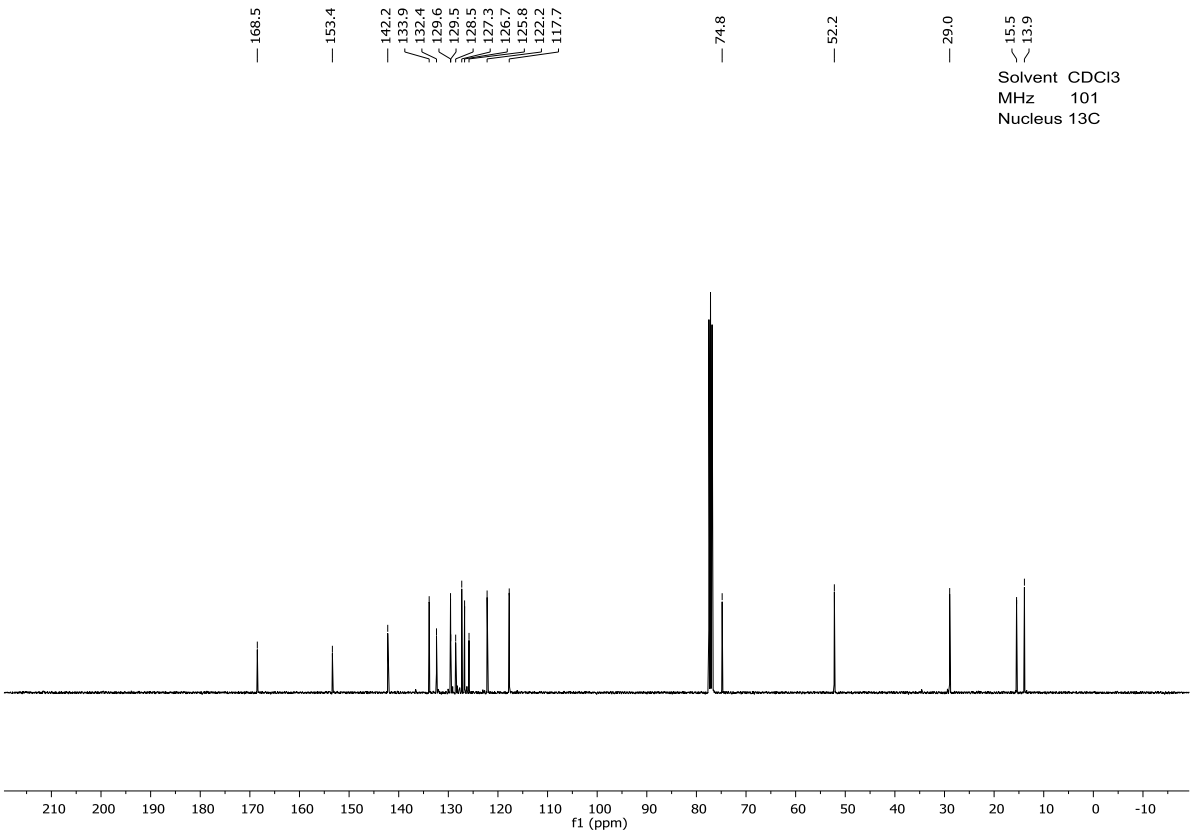
167.7
153.1
145.3
142.6
131.9
131.2
130.4
129.7
128.8
127.1
126.7
126.0
120.7
119.7
69.5
52.2
28.9
15.3
13.7

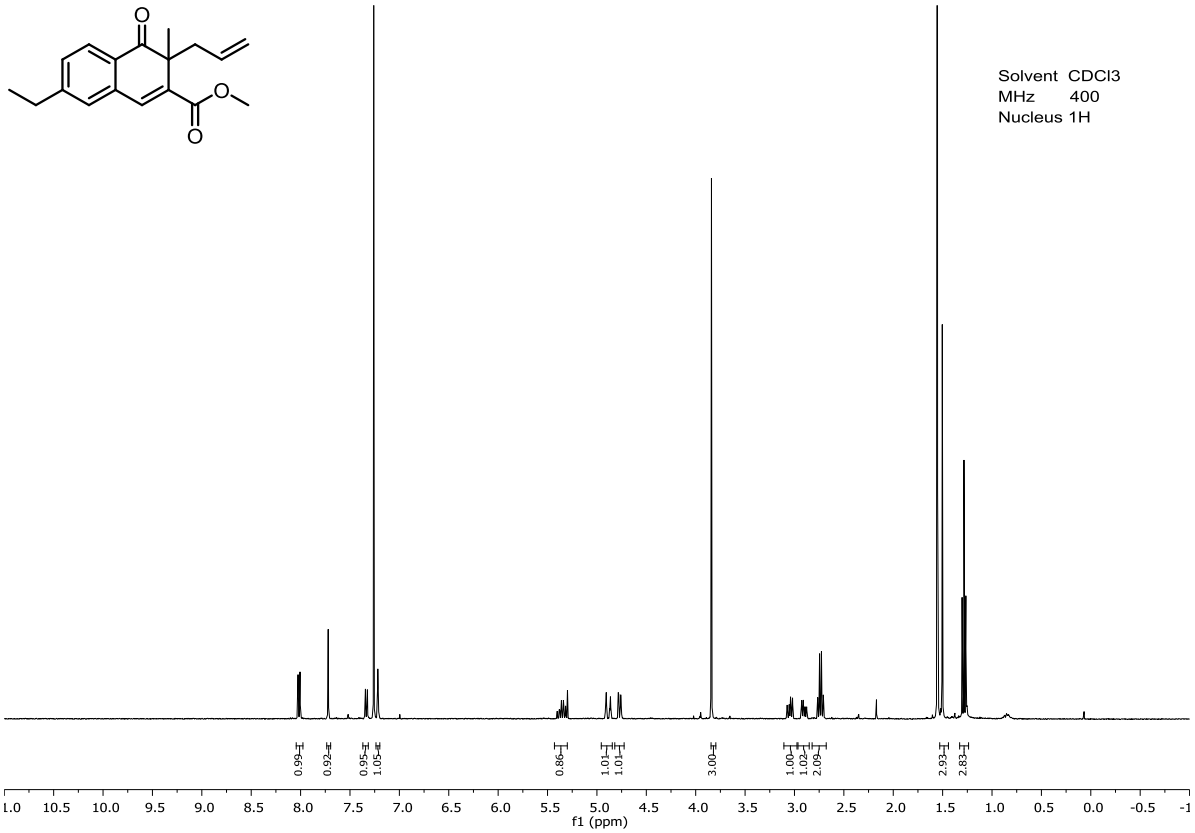
Solvent CDCl3
MHz 101
Nucleus 13C

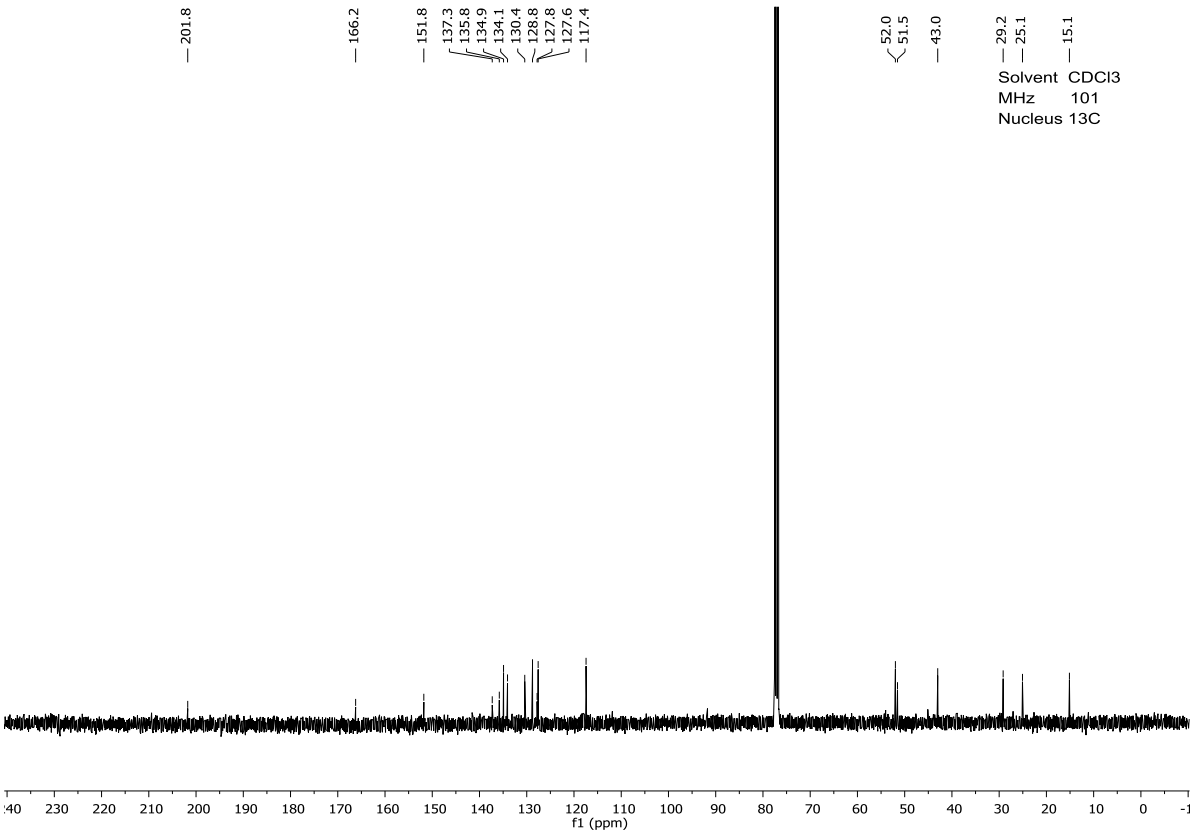


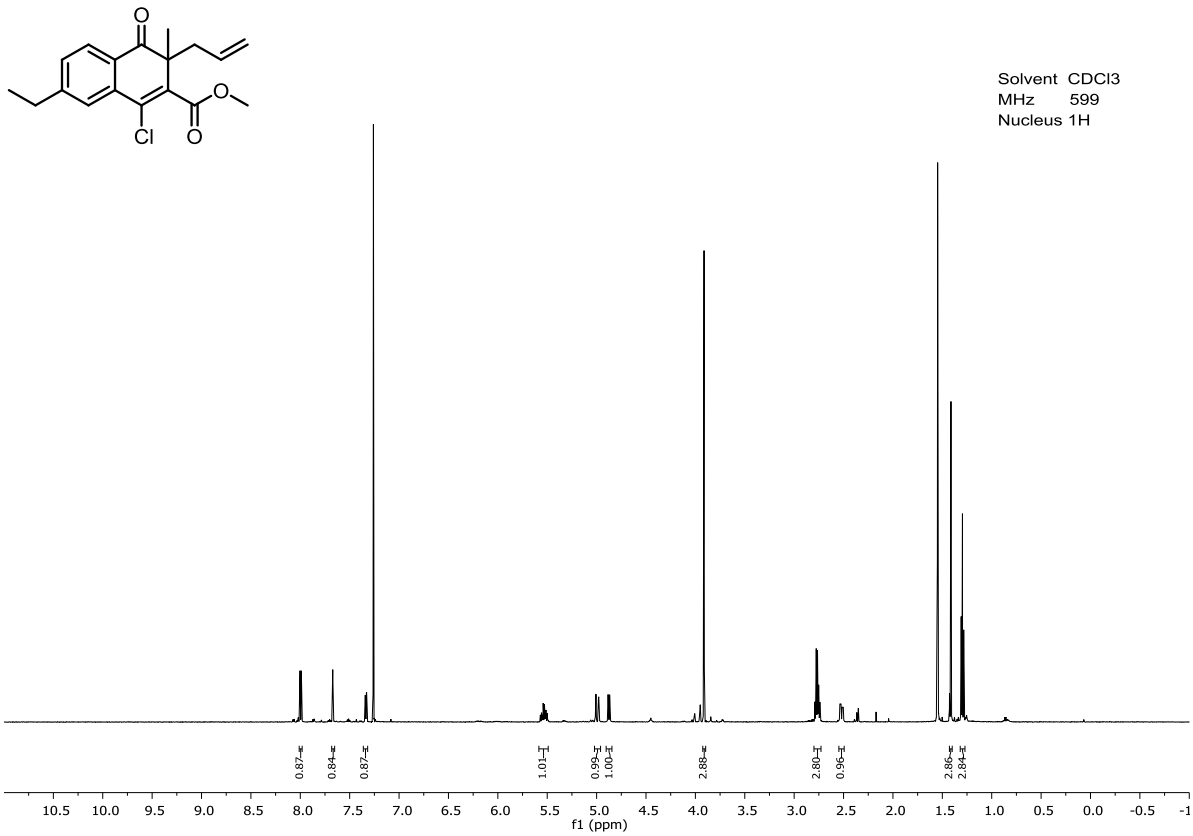


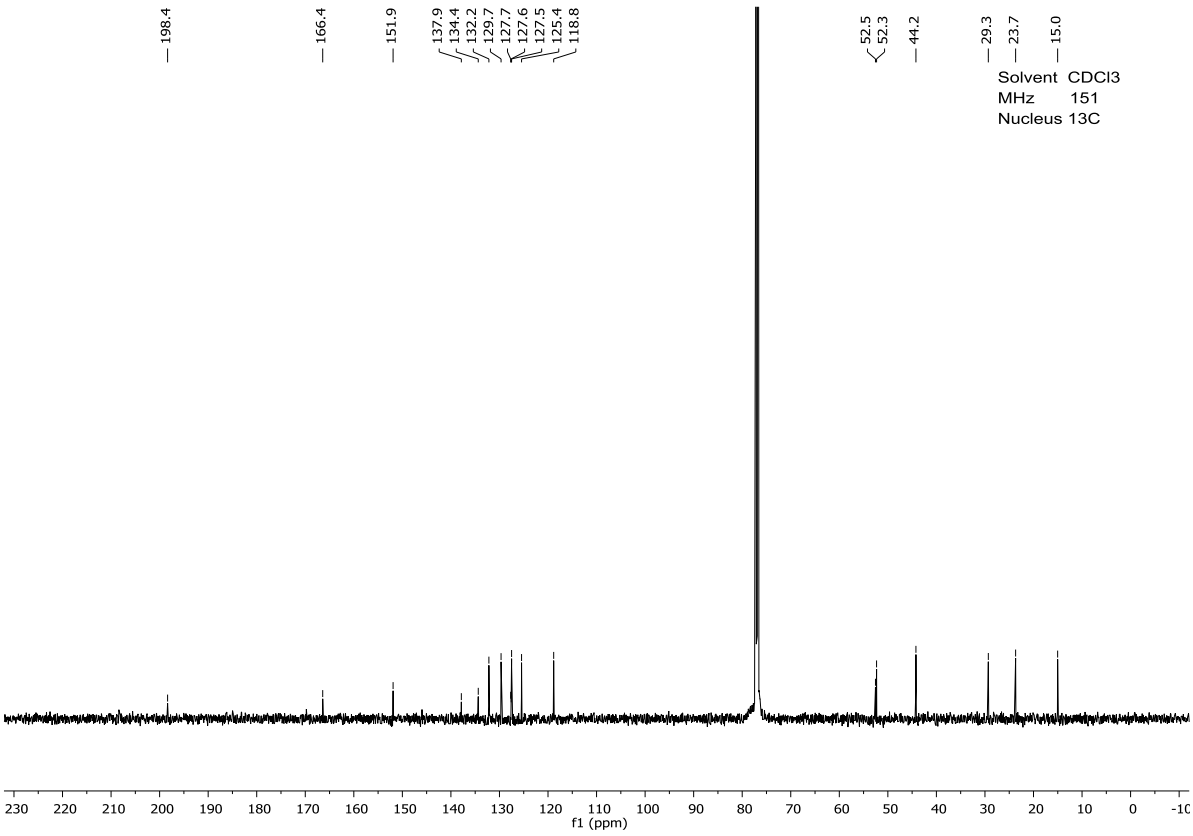
Solvent CDCl3
MHz 400
Nucleus 1H
0.89
0.93
0.96
0.95
0.96
1.00
1.00
2.06
3.00
1.99
2.97
2.93
f1 (ppm)

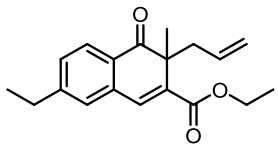

168.5
153.4
142.2
133.9
132.4
129.6
129.5
128.5
127.3
126.7
125.8
122.2
117.7
74.8
52.2
29.0
15.5
13.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

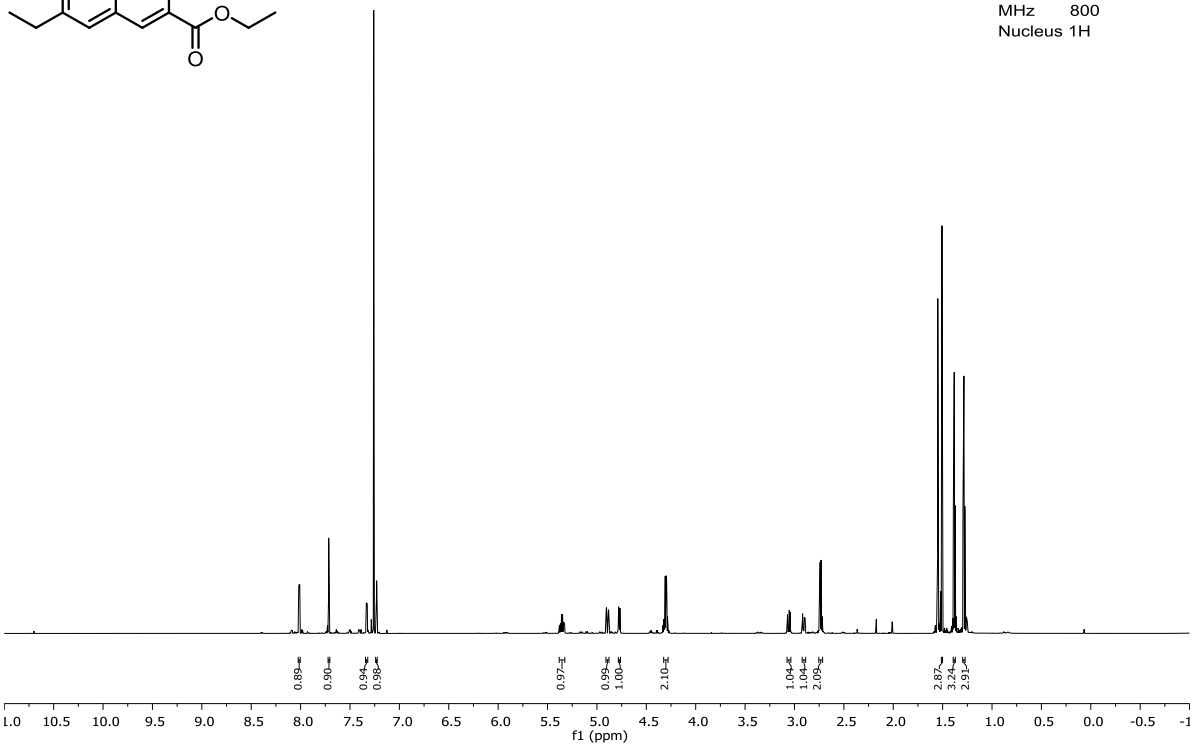

Solvent CDCl3
MHz 400
Nucleus 1H
0.99
0.92
0.95
1.05
0.86
1.01
1.01
3.00
1.00
1.02
2.09
2.93
2.83
f1 (ppm)

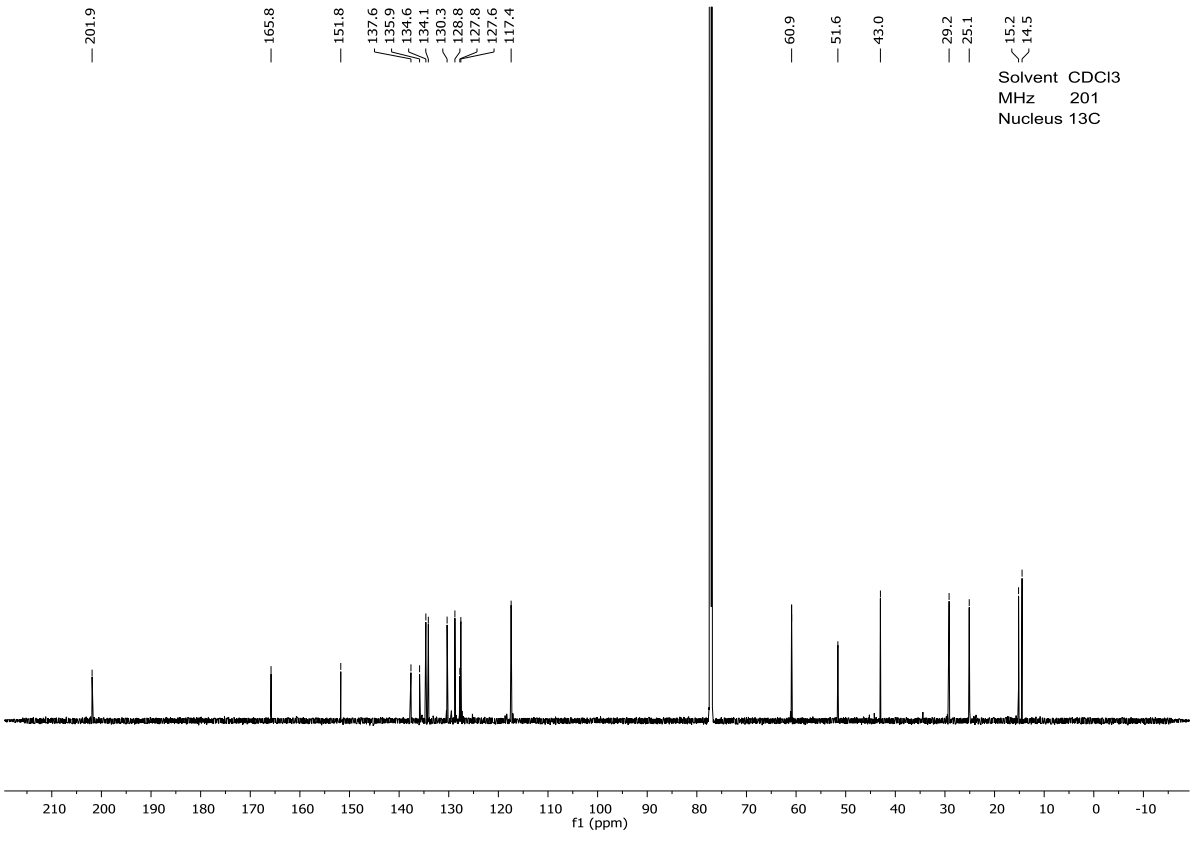

201.8
166.2
151.8
137.3
135.8
134.9
134.1
130.4
128.8
127.8
127.6
117.4
52.0
51.5
43.0
29.2
25.1
15.1
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

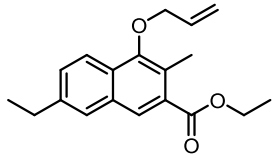

O
O
O
Cl
Solvent CDCl3
MHz 599
Nucleus 1H
0.87
0.84
0.87
1.01
0.99
1.00
2.88
2.80
0.96
2.86
2.84
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

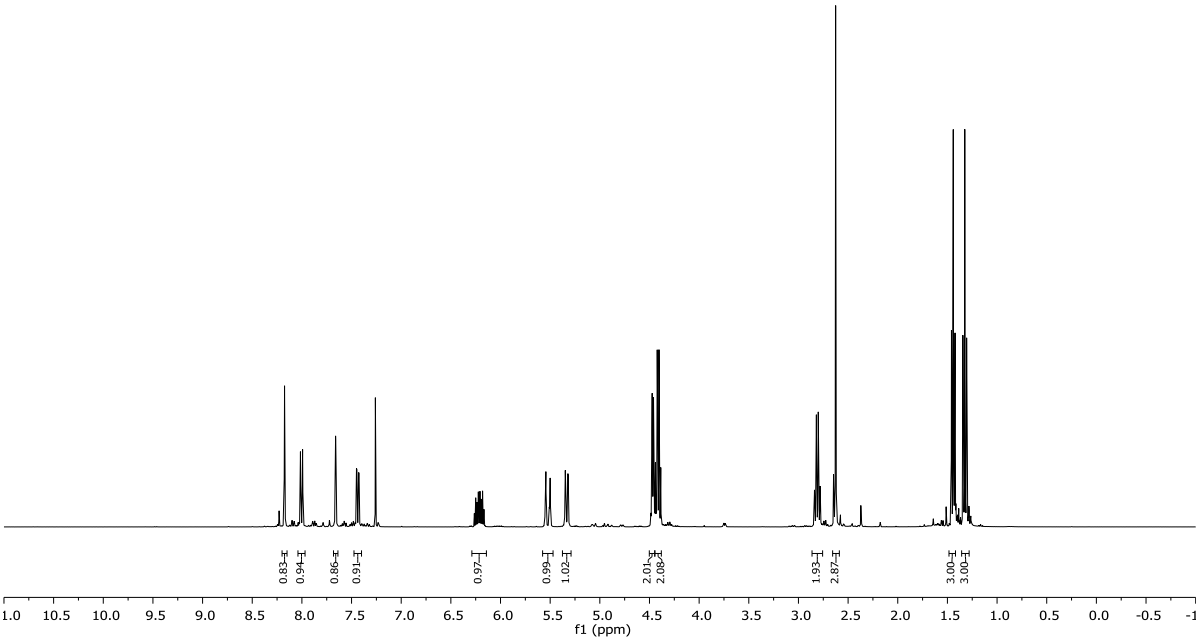

198.4
166.4
151.9
137.9
134.4
132.2
129.7
127.7
127.6
127.5
125.4
118.8
52.5
52.3
44.2
29.3
23.7
15.0
Solvent CDCl3
MHz 151
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

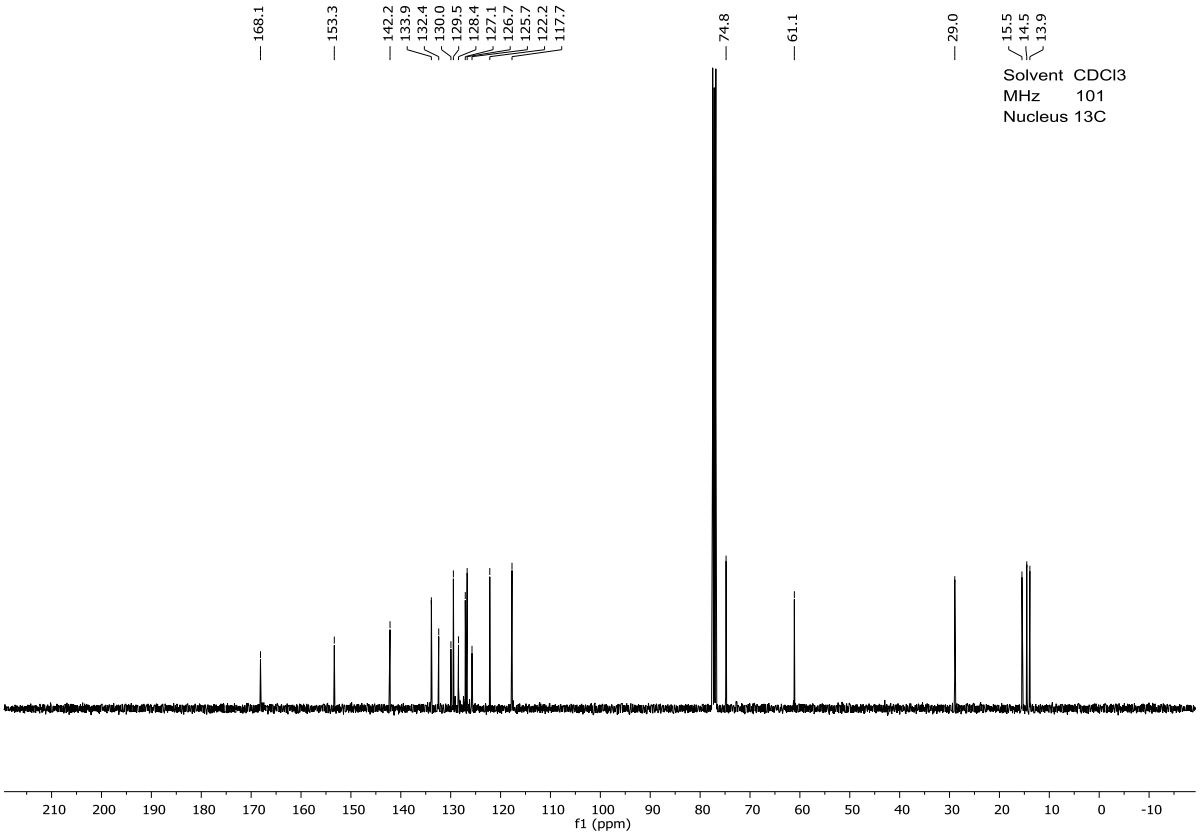


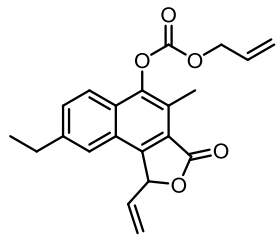

Solvent CDCl3
MHz 800
Nucleus 1H
0.89
0.90
0.94
0.98
0.97
0.99
1.00
2.10
1.04
1.04
2.09
2.87
3.24
2.91
f1 (ppm)


201.9
165.8
151.8
137.6
135.9
134.6
134.1
130.3
128.8
127.8
127.6
117.4
60.9
51.6
43.0
29.2
25.1
15.2
14.5
Solvent CDCl3
MHz 201
Nucleus 13C
f1 (ppm)

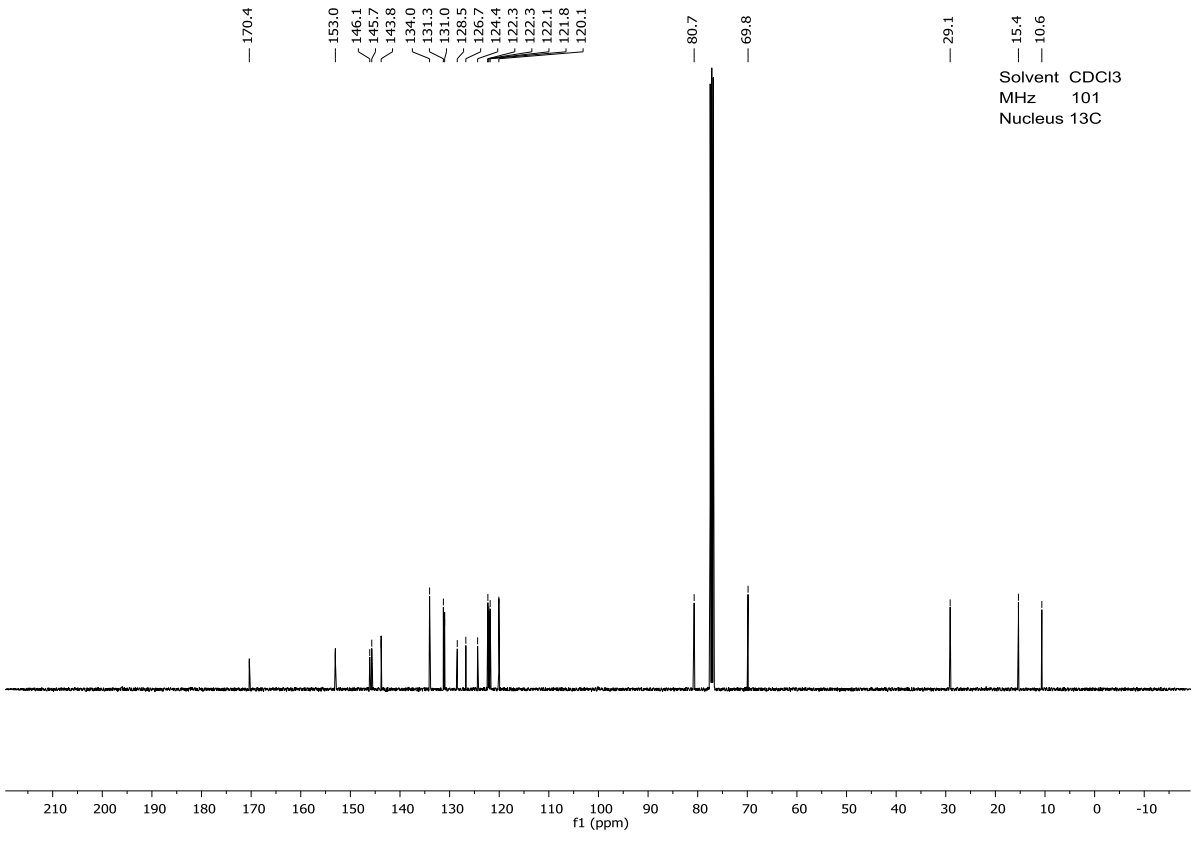


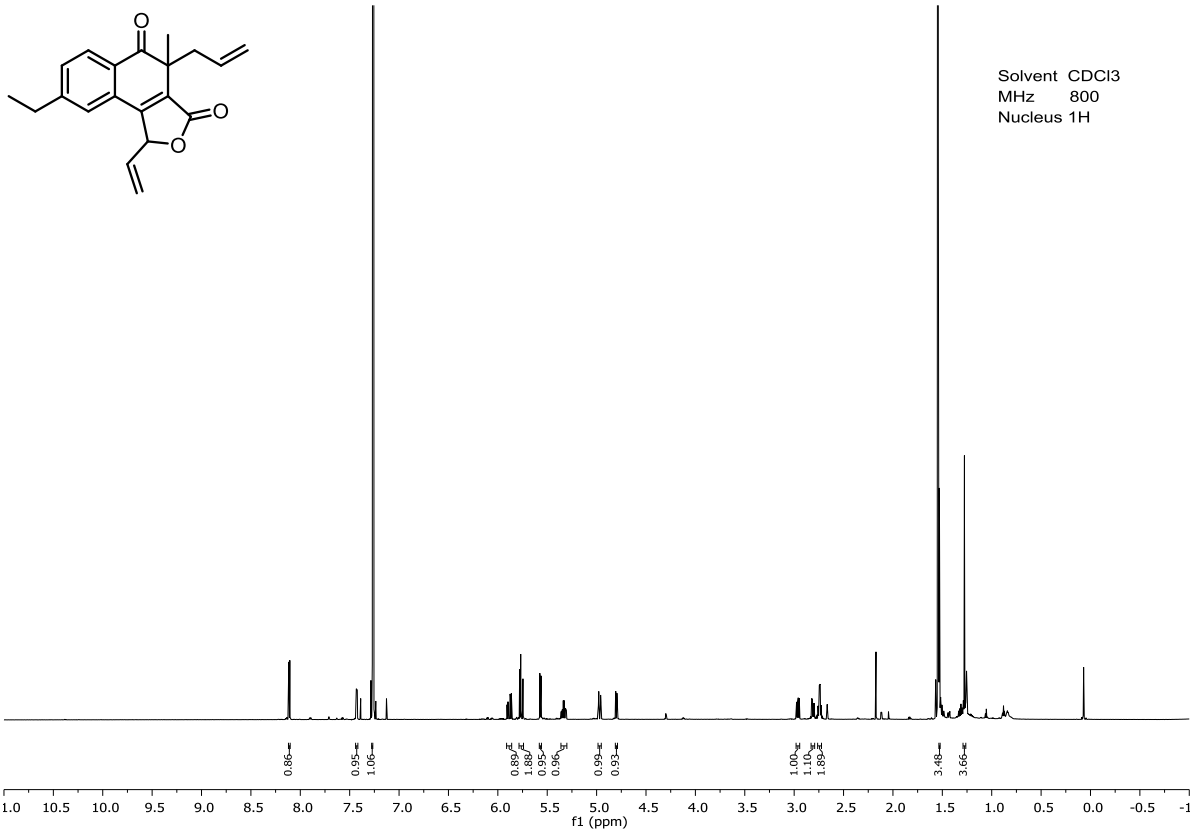

Solvent CDCl3
MHz 400
Nucleus 1H
0.83
0.94
0.86
0.91
0.97
0.99
1.02
2.01
2.08
1.93
2.87
3.00
3.00
f1 (ppm)

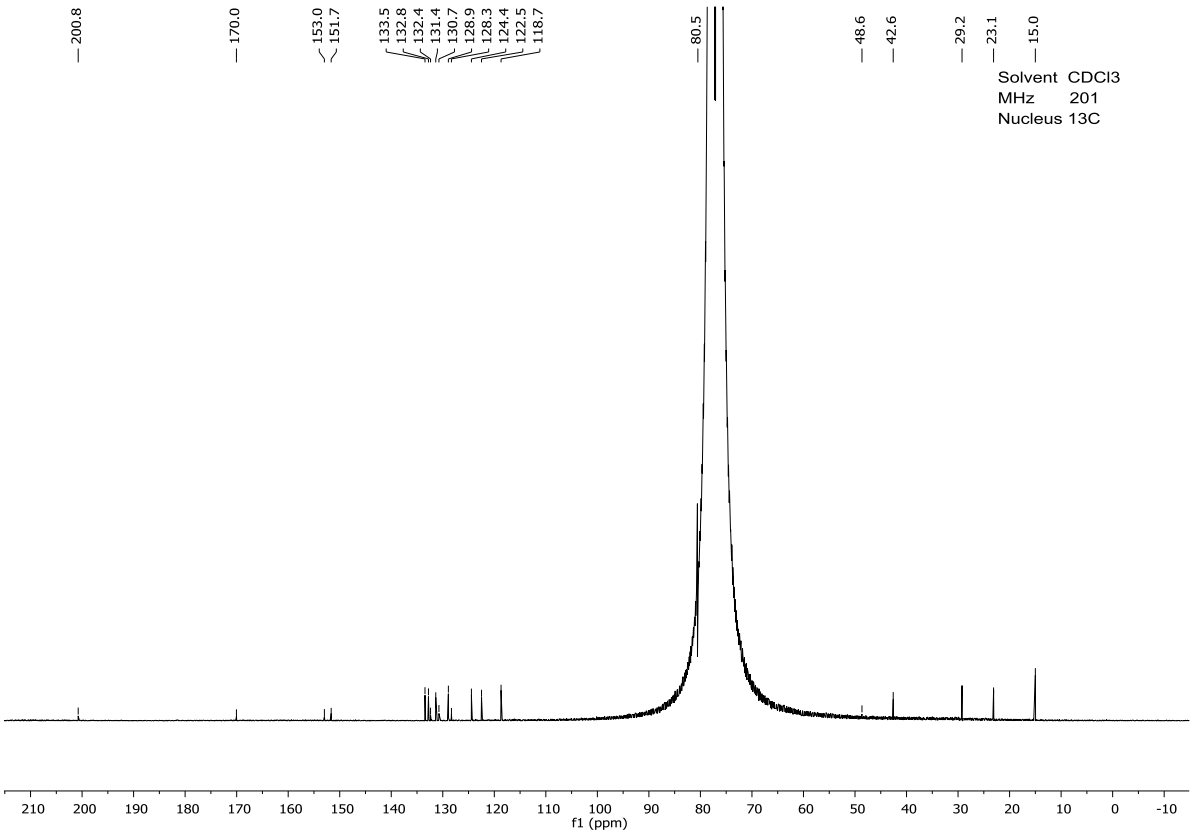

168.1
153.3
142.2
133.9
132.4
130.0
129.5
128.4
127.1
126.7
125.7
122.2
117.7
74.8
61.1
29.0
15.5
14.5
13.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

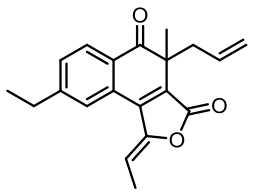


Solvent CDCl3
MHz 400
Nucleus 1H
1.01
1.00
1.02
1.05
2.05
1.05
1.00
0.98
0.97
2.04
2.12
3.13
3.21
f1 (ppm)

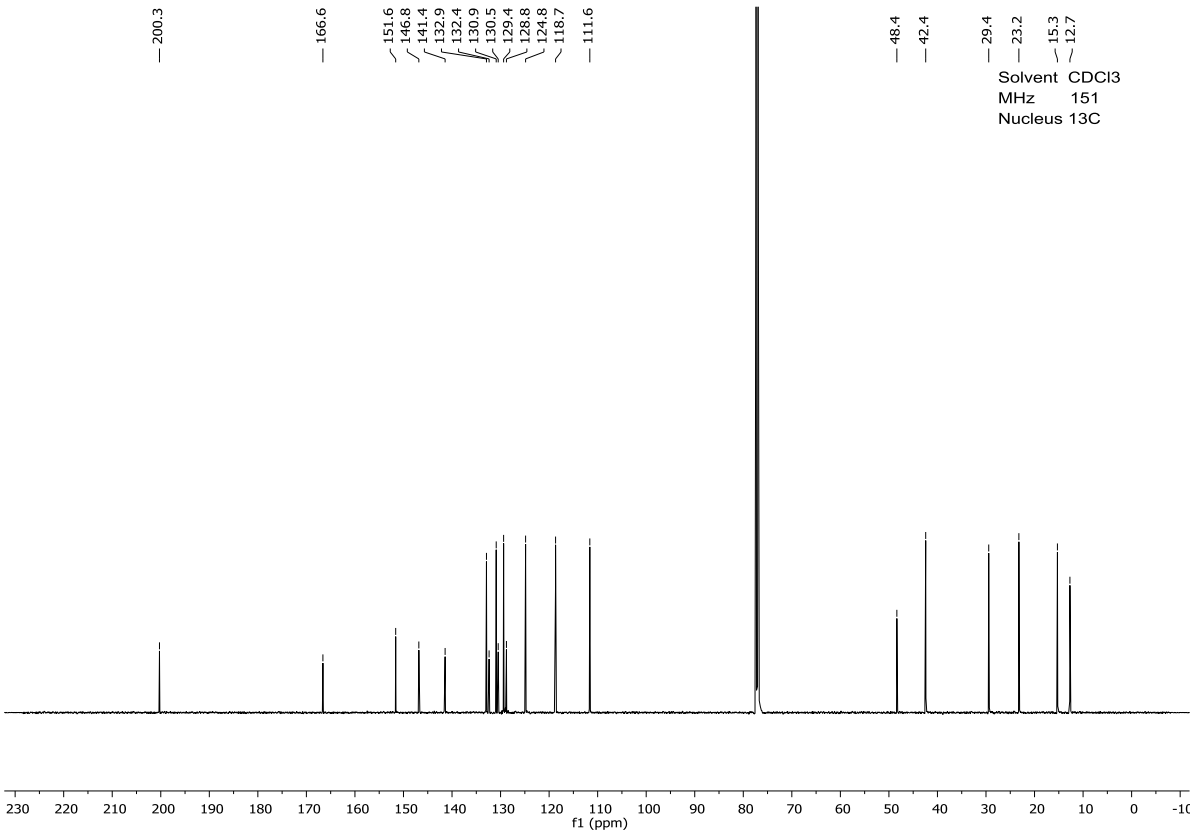

170.4
153.0
146.1
145.7
143.8
134.0
131.3
131.0
128.5
126.7
124.4
122.3
122.3
122.1
121.8
120.1
80.7
69.8
29.1
15.4
10.6
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

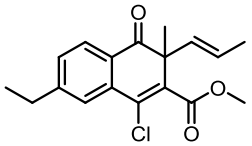

Solvent CDCl3
MHz 800
Nucleus 1H
0.86
0.95
1.06
0.89
1.88
0.95
0.96
0.99
0.93
1.00
1.10
1.89
3.48
3.66
f1 (ppm)


200.8
170.0
153.0
151.7
133.5
132.8
132.4
131.4
130.7
128.9
128.3
124.4
122.5
118.7
80.5
48.6
42.6
29.2
23.1
15.0
Solvent CDCl3
MHz 201
Nucleus 13C
f1 (ppm)

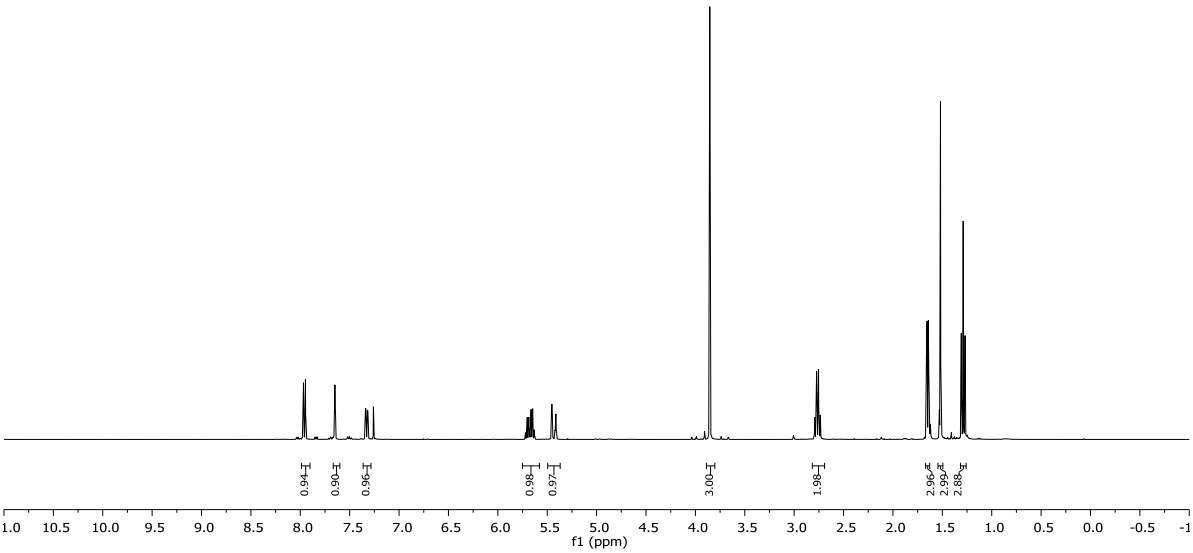


Solvent CDCl3
MHz 599
Nucleus 1H
0.97
1.00
1.00
1.01
0.98
1.01
1.01
1.04
1.04
2.03
2.96
3.03
2.93
f1 (ppm)


200.3
166.6
151.6
146.8
141.4
132.9
132.4
130.9
130.5
129.4
128.8
124.8
118.7
111.6
48.4
42.4
29.4
23.2
15.3
12.7
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

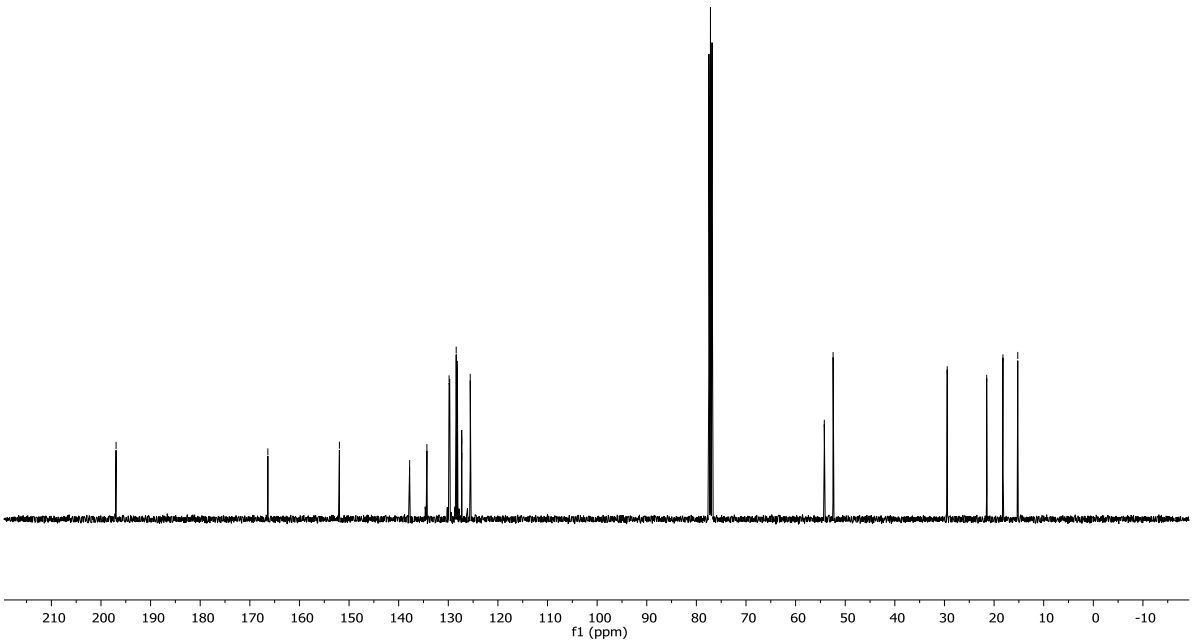


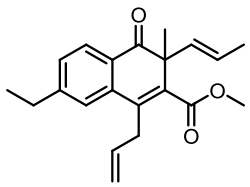
Solvent CDCl3
MHz 400
Nucleus 1H



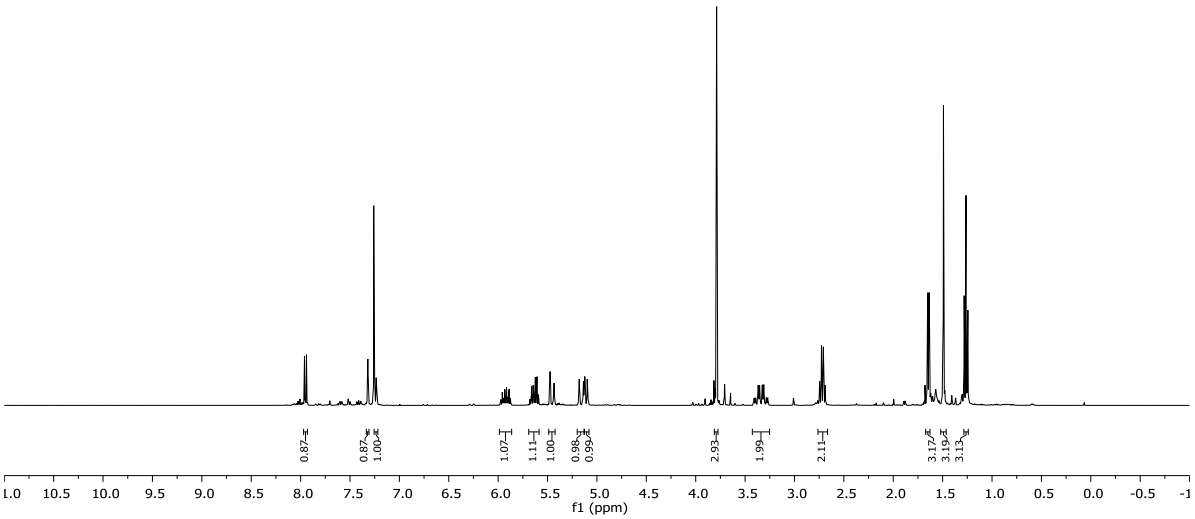
197.0
166.4
151.9
137.8
134.3
129.8
129.7
128.4
128.2
127.3
127.3
125.6
54.2
52.4
29.4
21.5
18.2
15.2

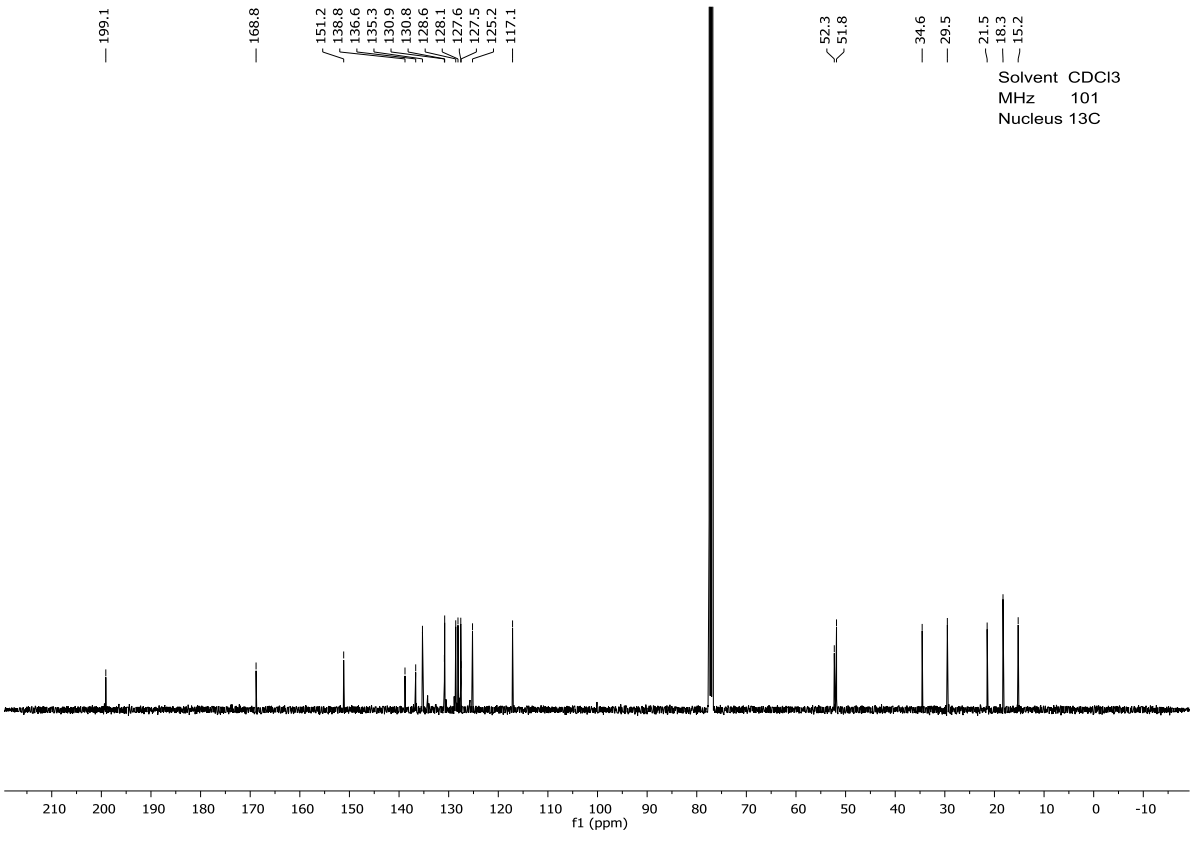
Solvent CDCl3
MHz 101
Nucleus 13C



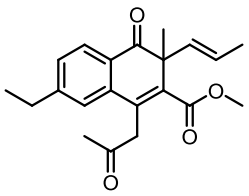


Solvent CDCl3
MHz 400
Nucleus 1H

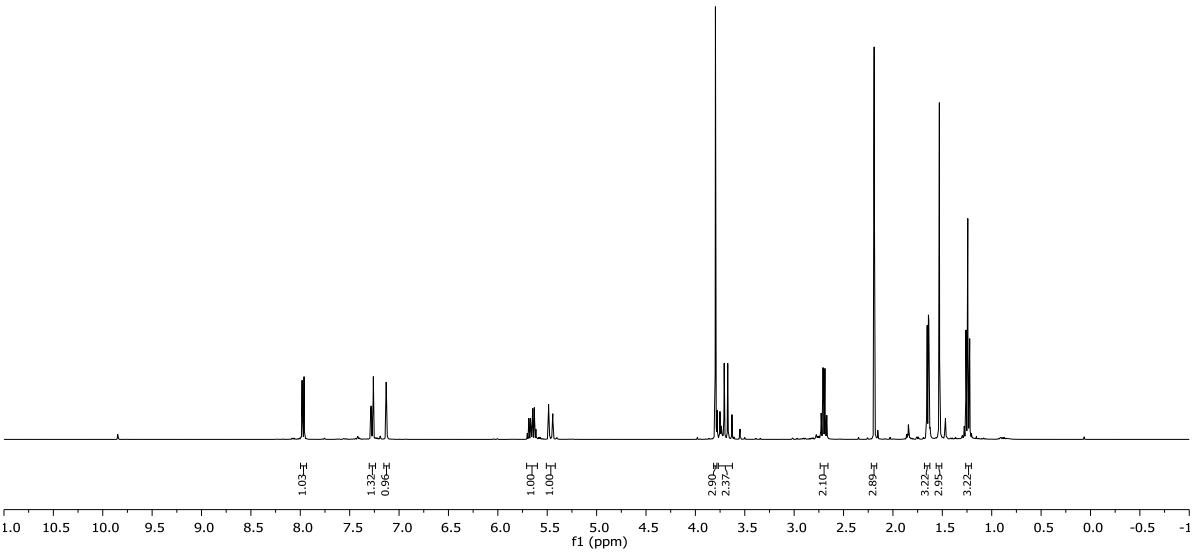




Solvent CDCl3
MHz 101
Nucleus 13C

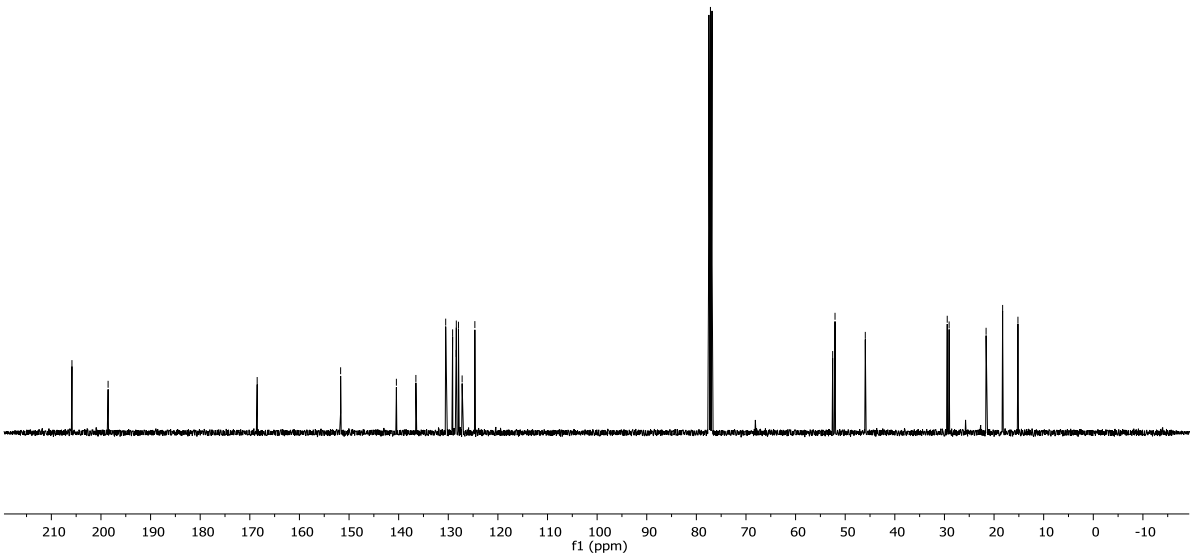


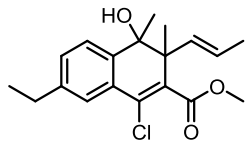
Solvent CDCl3
MHz 400
Nucleus 1H



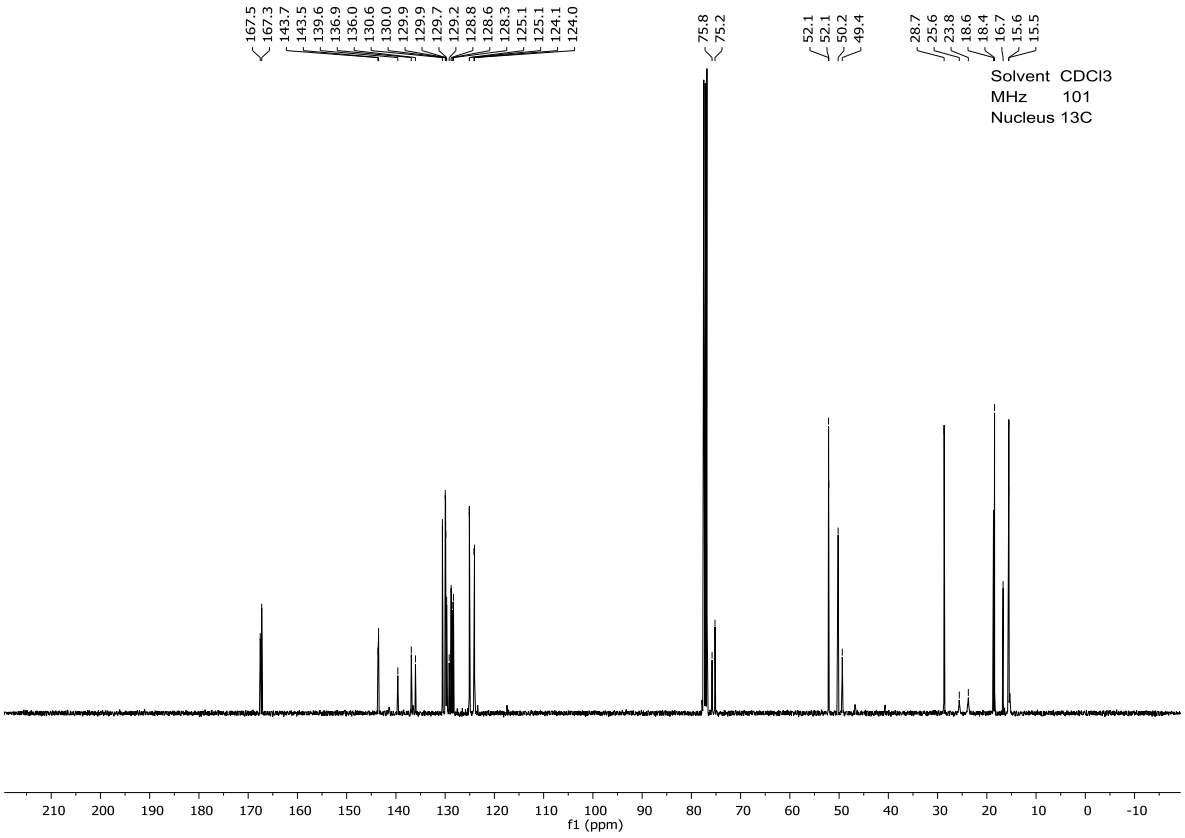
205.8
198.6
168.5
151.7
140.5
136.5
130.5
129.1
128.4
128.4
127.9
127.2
124.6
52.5
52.1
46.0
29.4
29.1
21.6
18.3
15.2

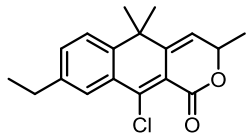
Solvent CDCl3
MHz 101
Nucleus 13C



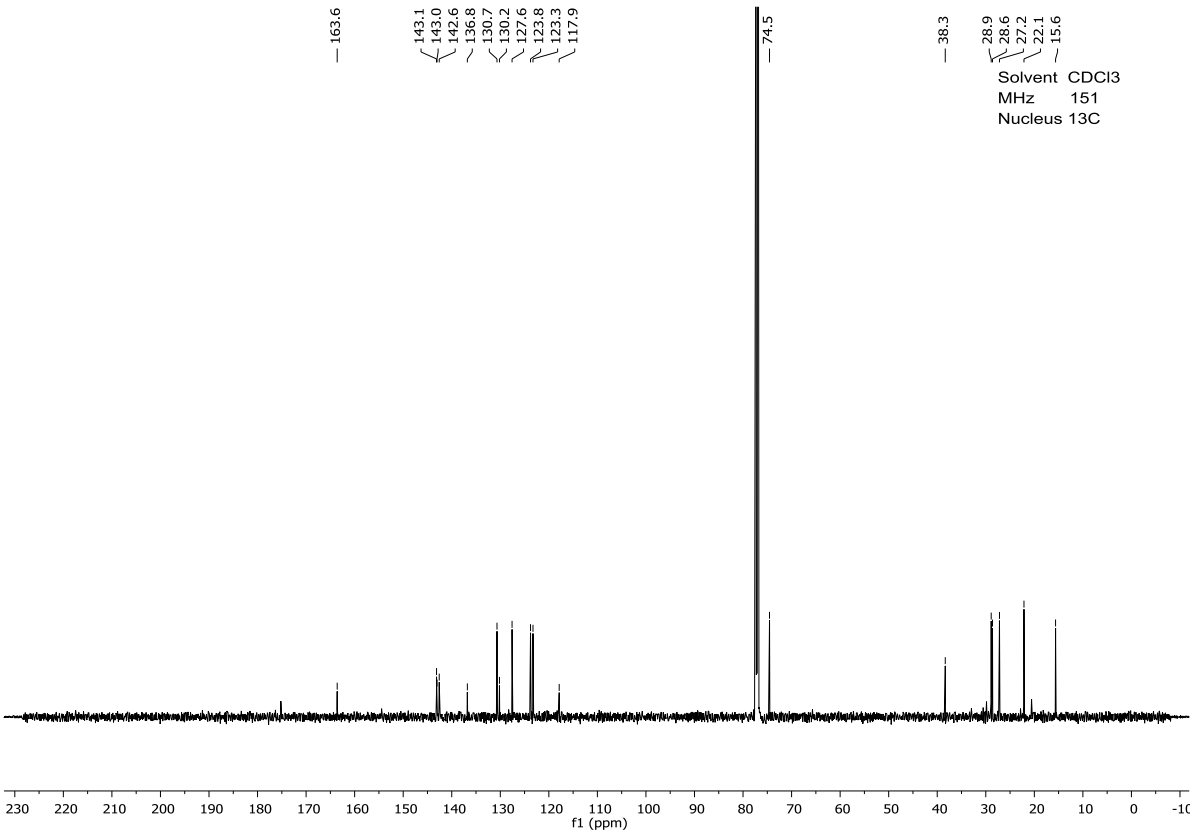

HO
Cl
O
O

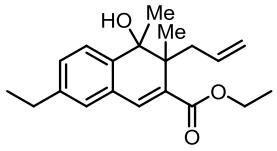
Solvent CDCl3
MHz 400
Nucleus 1H
3.86
2.03
2.71
1.06
3.00
2.31
3.73
1.07
0.81
2.45
3.20
2.34
3.16
11.62
f1 (ppm)


167.5
167.3
143.7
143.5
139.6
136.9
136.0
130.6
130.0
129.9
129.9
129.7
129.2
128.8
128.6
128.3
125.1
125.1
124.1
124.0
75.8
75.2
52.1
52.1
50.2
49.4
28.7
25.6
23.8
18.6
18.4
16.7
15.6
15.5
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

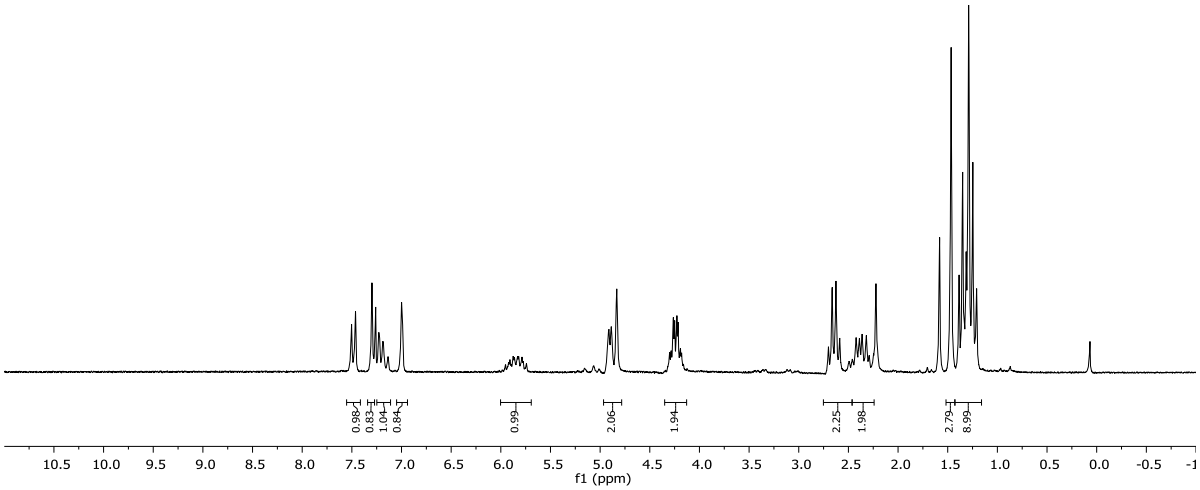

Cl
O
O

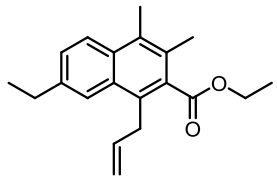
Solvent CDCl3
MHz 599
Nucleus 1H
0.88
0.95
0.92
0.91
0.96
2.00
5.89
2.83
3.51
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

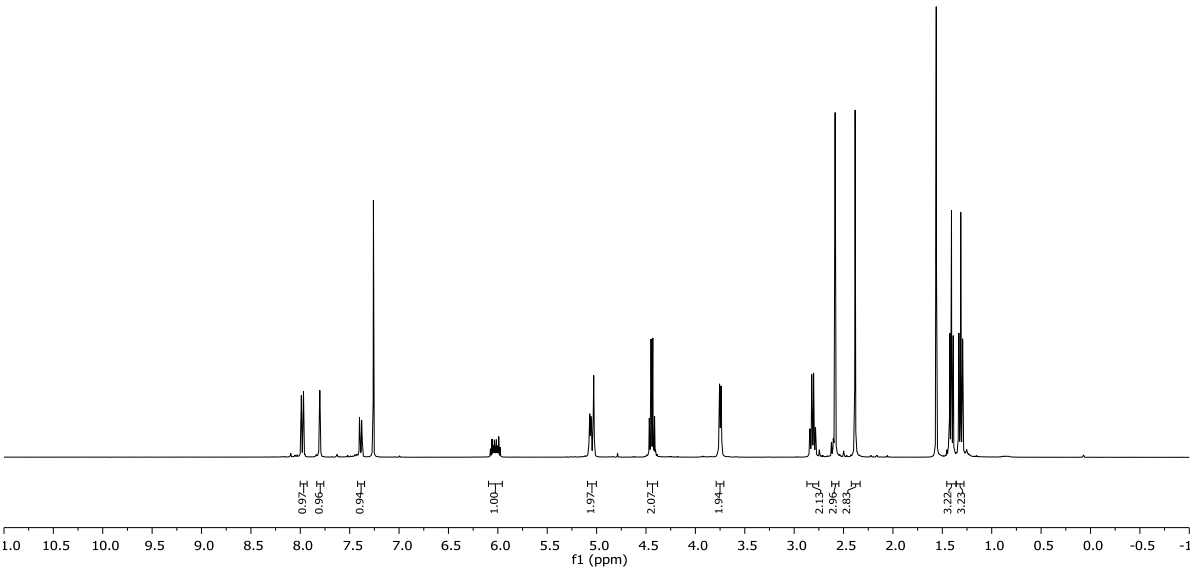

163.6
143.1
143.0
142.6
136.8
130.7
130.2
127.6
123.8
123.3
117.9
74.5
38.3
28.9
28.6
27.2
22.1
15.6
Solvent CDCl3
MHz 151
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

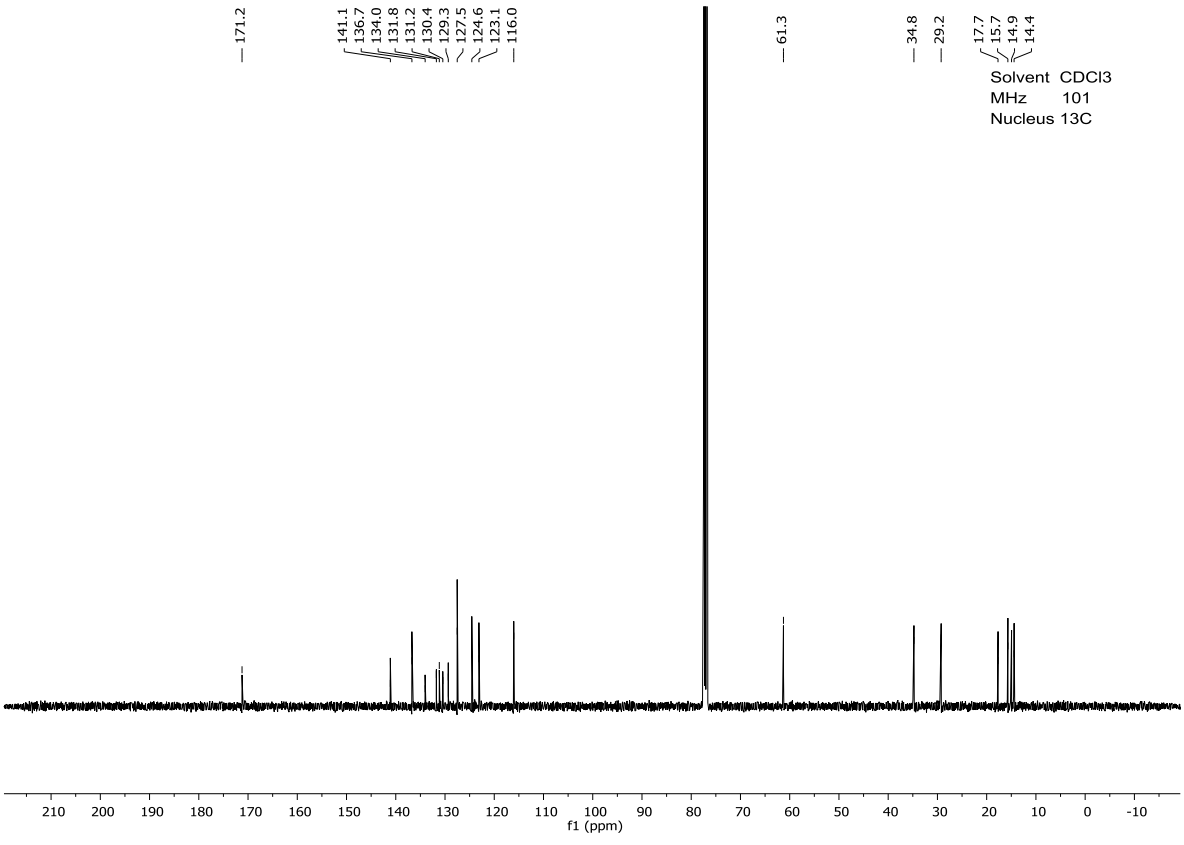


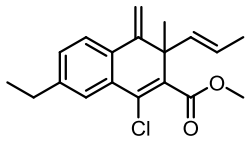
Solvent CDCl3
MHz 200
Nucleus 1H



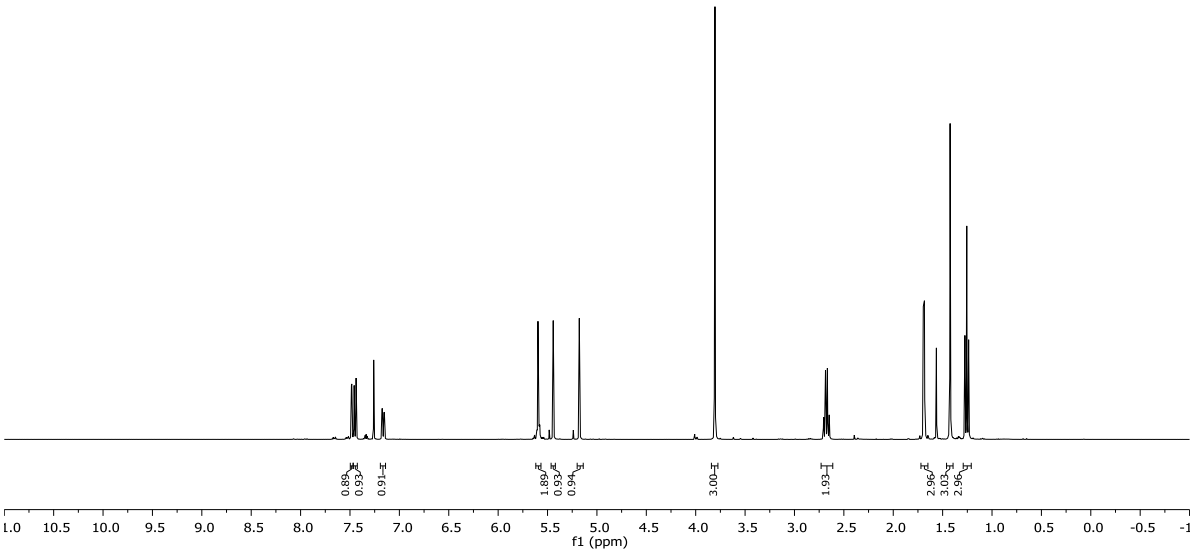


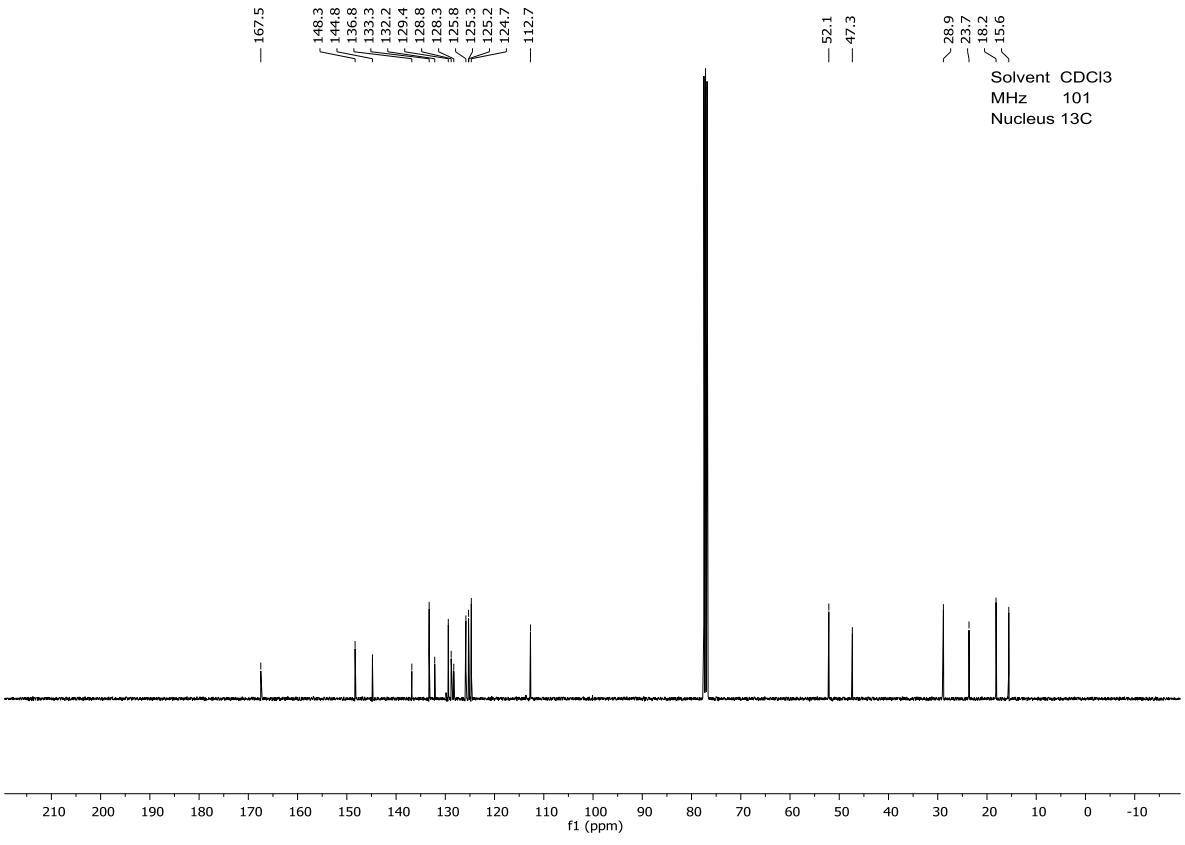

Solvent CDCl3
MHz 400
Nucleus 1H
0.97
0.96
0.94
1.00
1.97
2.07
1.94
2.13
2.96
2.83
3.22
3.23
f1 (ppm)


171.2
141.1
136.7
134.0
131.8
131.2
130.4
129.3
127.5
124.6
123.1
116.0
61.3
34.8
29.2
17.7
15.7
14.9
14.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

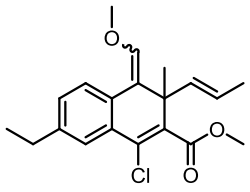


Solvent CDCl3
MHz 400
Nucleus 1H

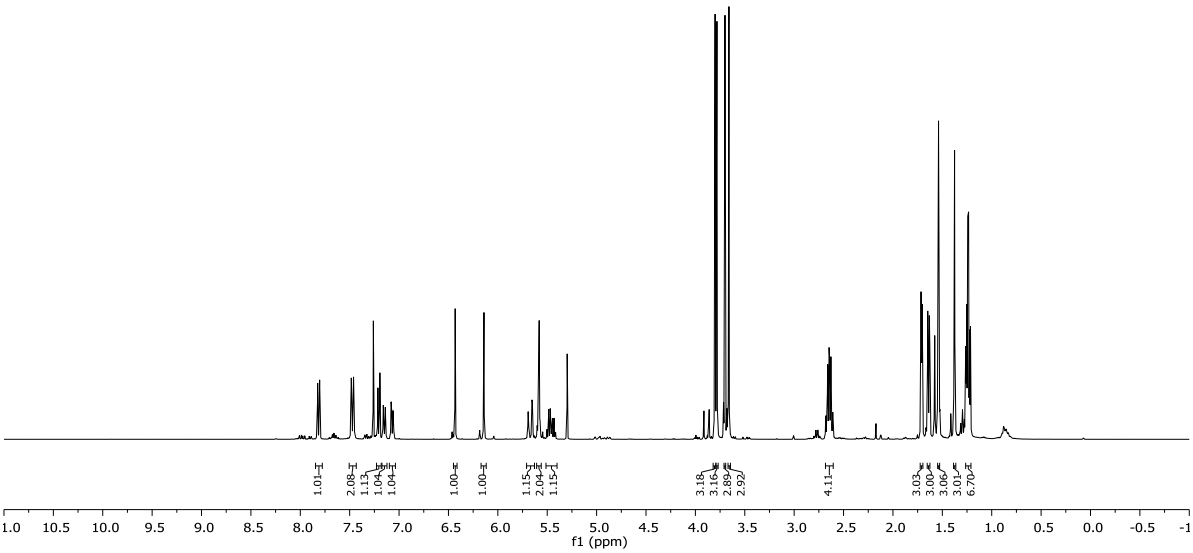


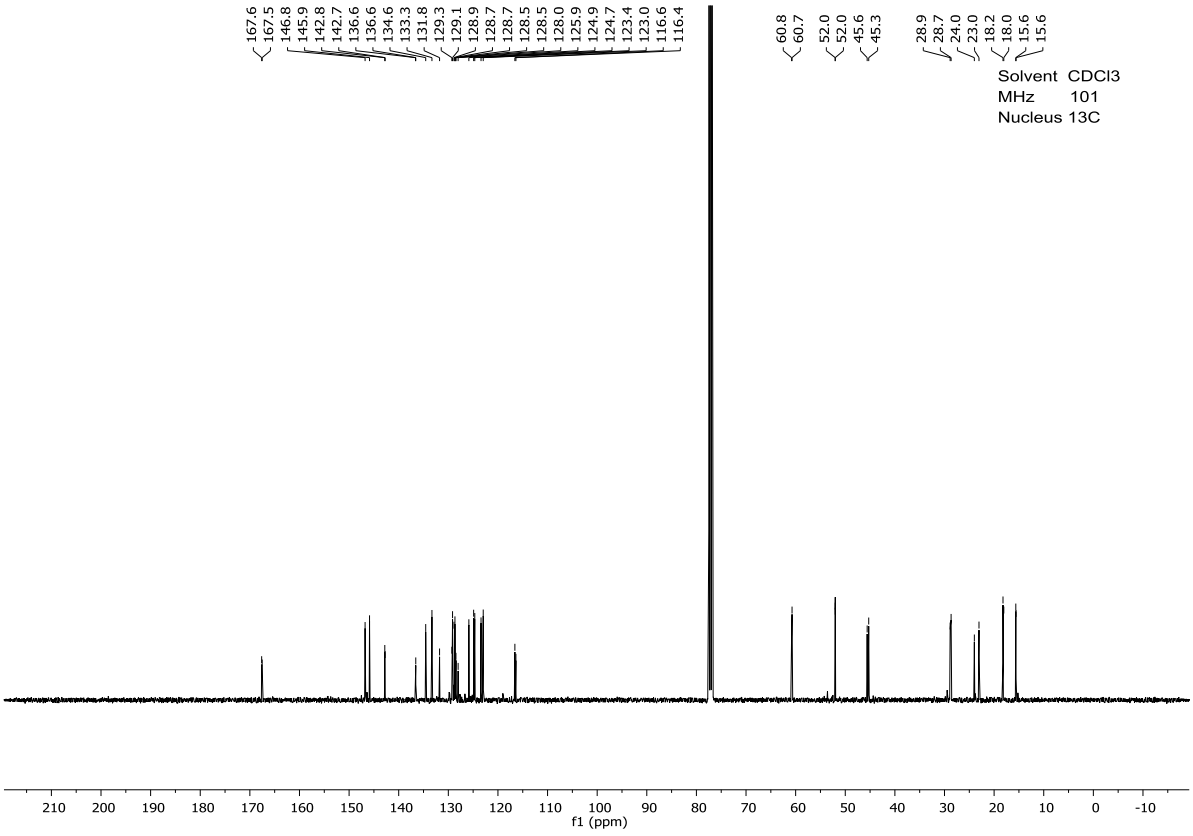


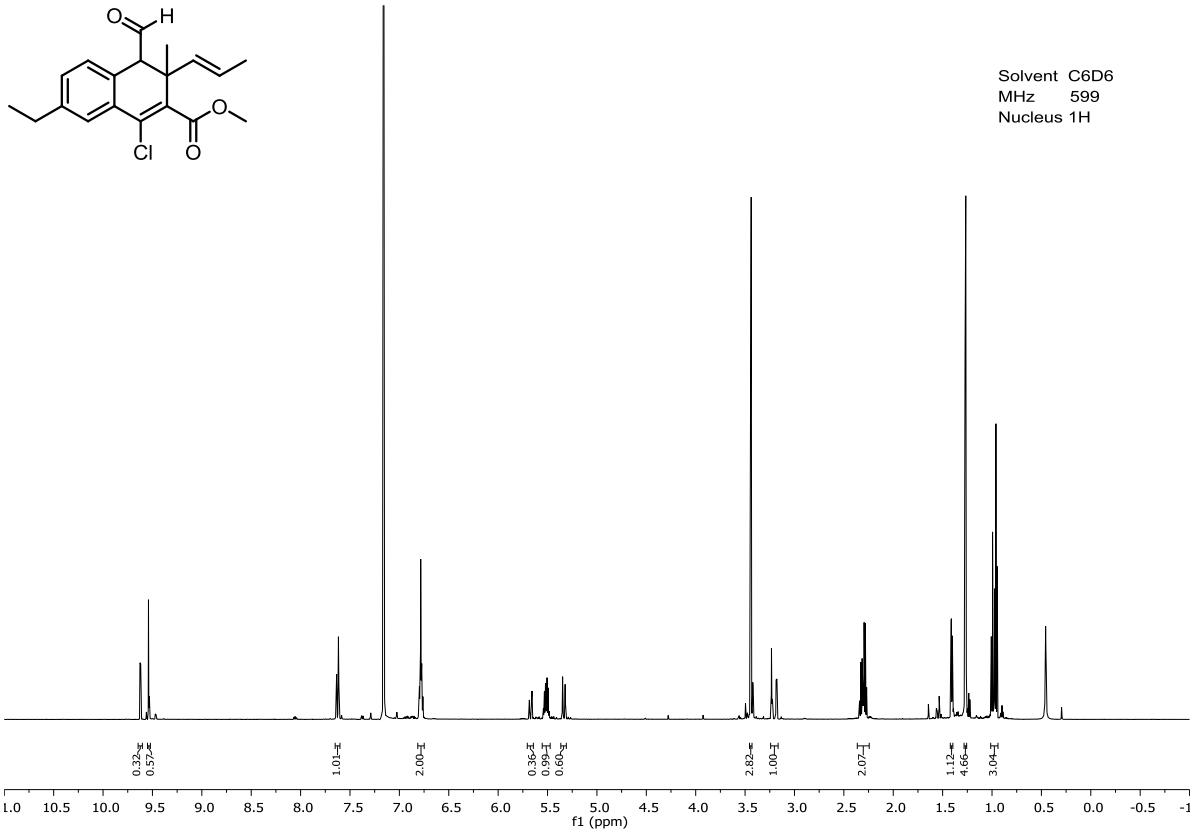
Solvent CDCl3
MHz 101
Nucleus 13C

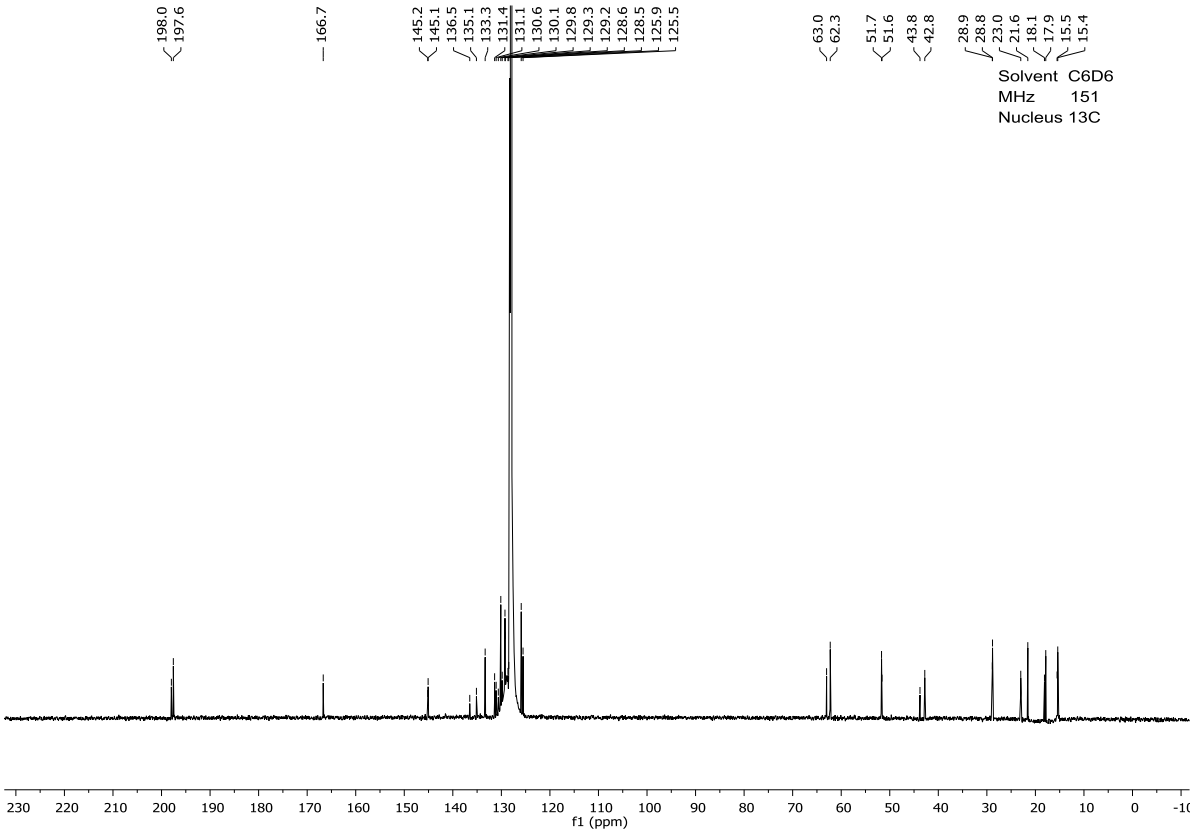


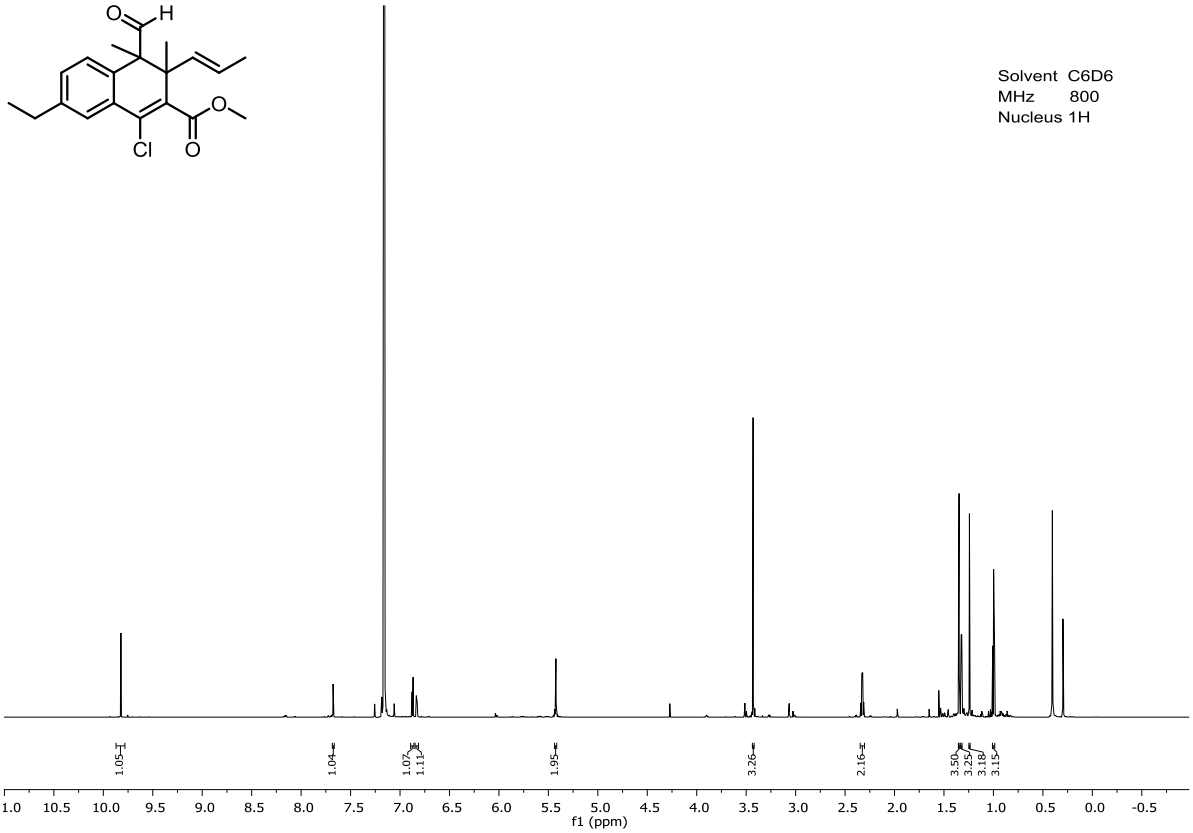
Solvent CDCl3
MHz 400
Nucleus 1H

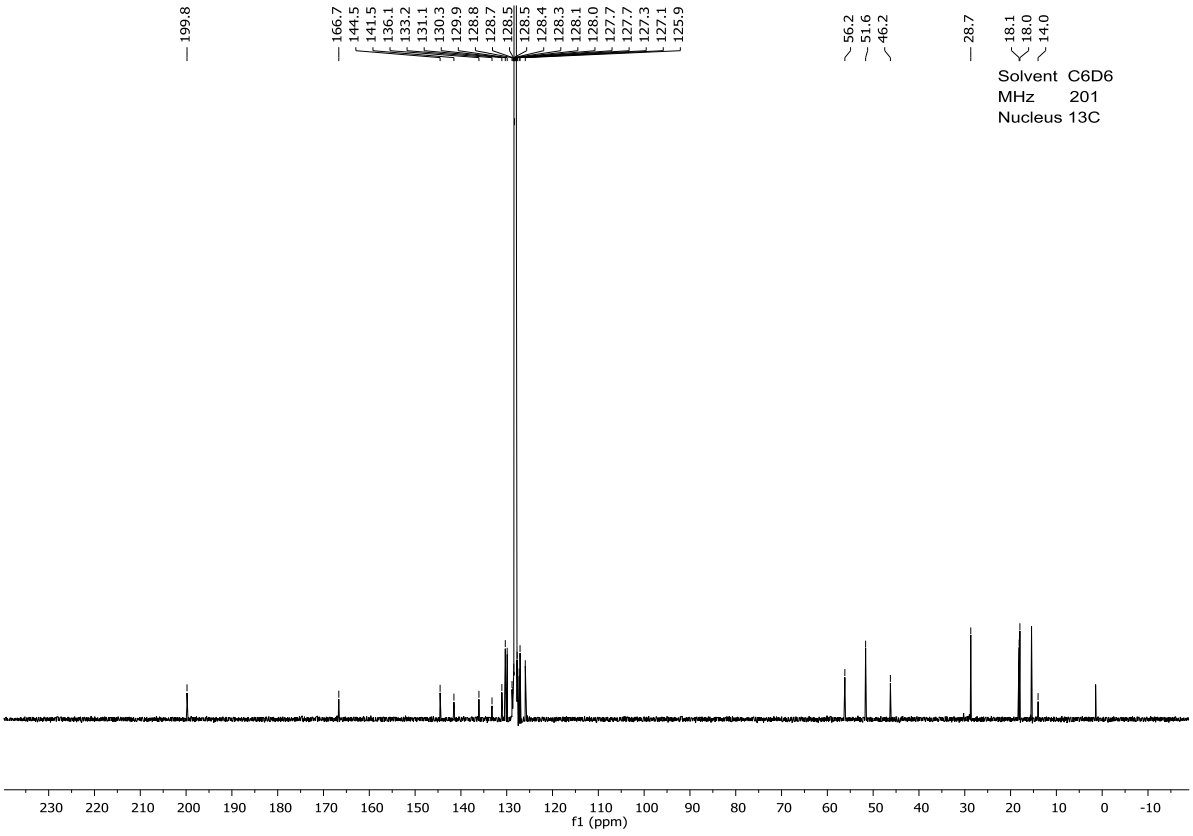


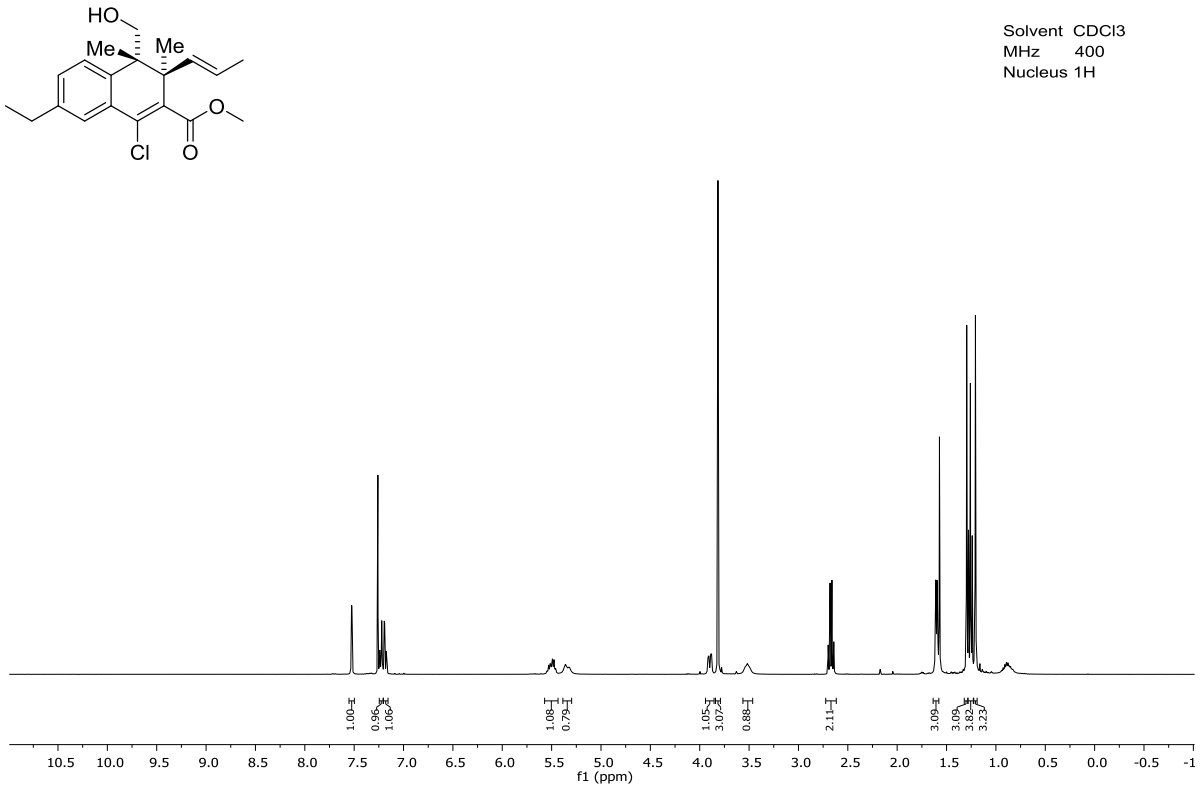


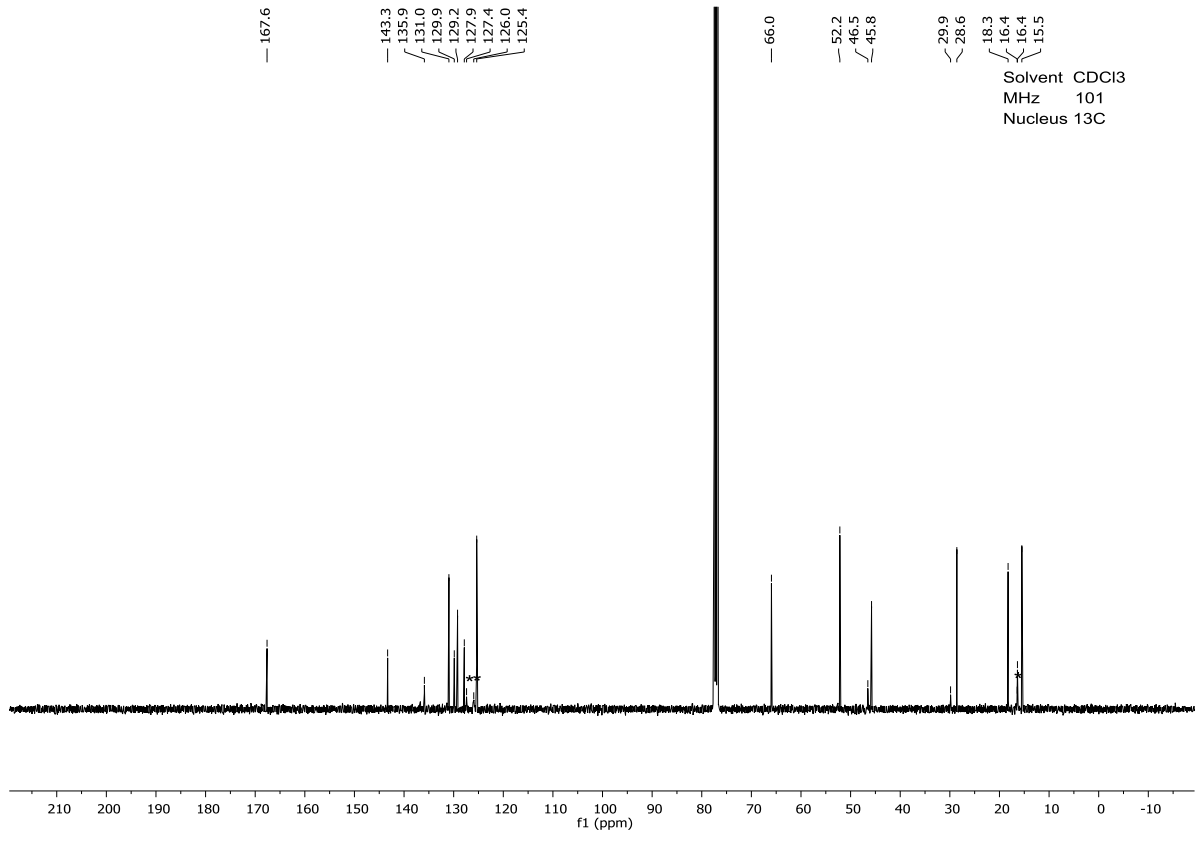

Solvent C6D6
MHz 599
Nucleus 1H
0.32
0.57
1.01
2.00
0.36
0.99
0.60
2.82
1.00
2.07
1.12
4.66
3.04
f1 (ppm)

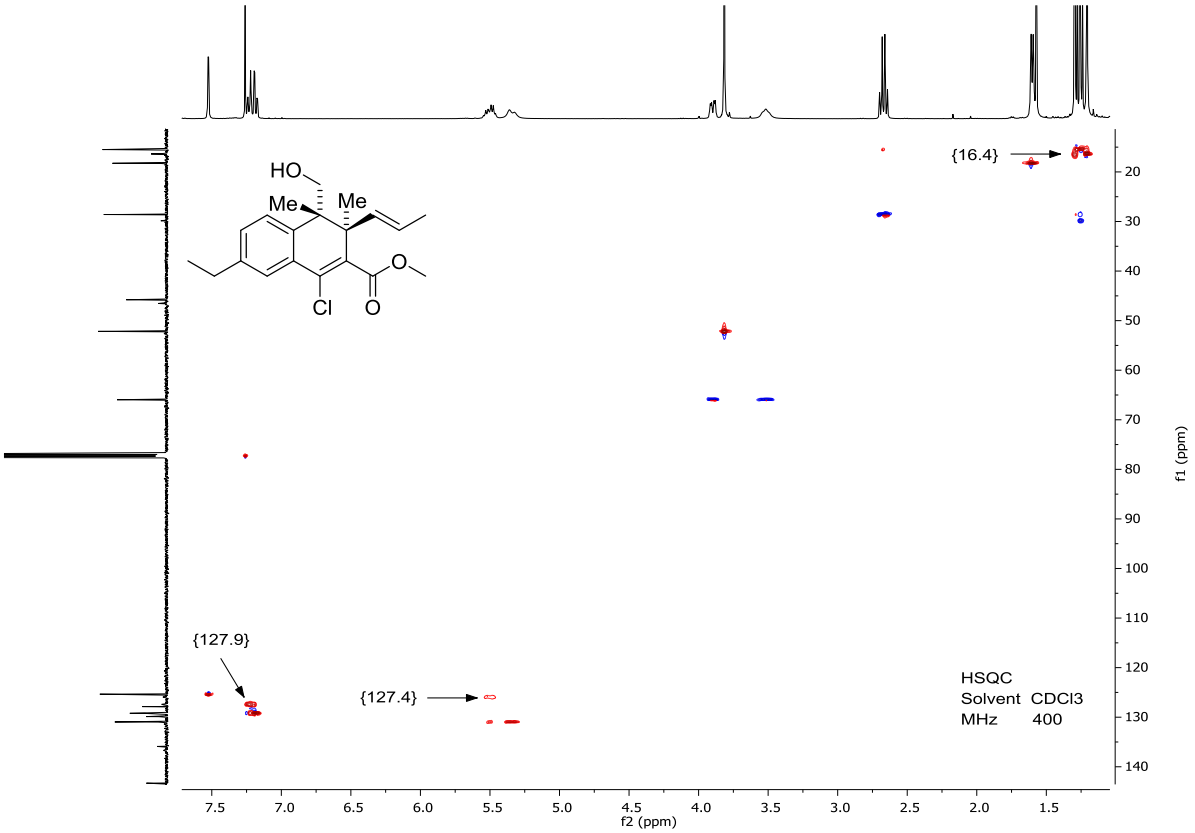

198.0
197.6
166.7
145.2
145.1
136.5
135.1
133.3
131.4
131.1
130.6
130.1
129.8
129.3
129.2
128.6
128.5
125.9
125.5
63.0
62.3
51.7
51.6
43.8
42.8
28.9
28.8
23.0
21.6
18.1
17.9
15.5
15.4
Solvent C6D6
MHz 151
Nucleus 13C
f1 (ppm)

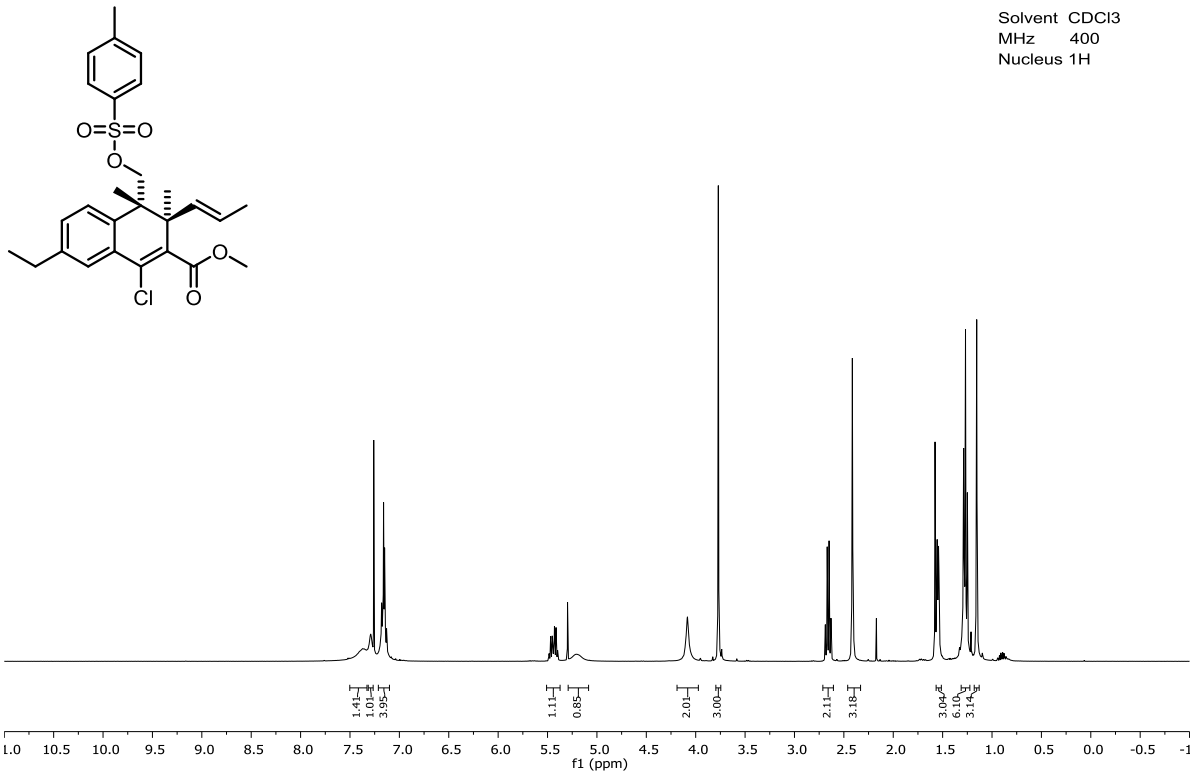

Solvent C6D6
MHz 800
Nucleus 1H
f1 (ppm)

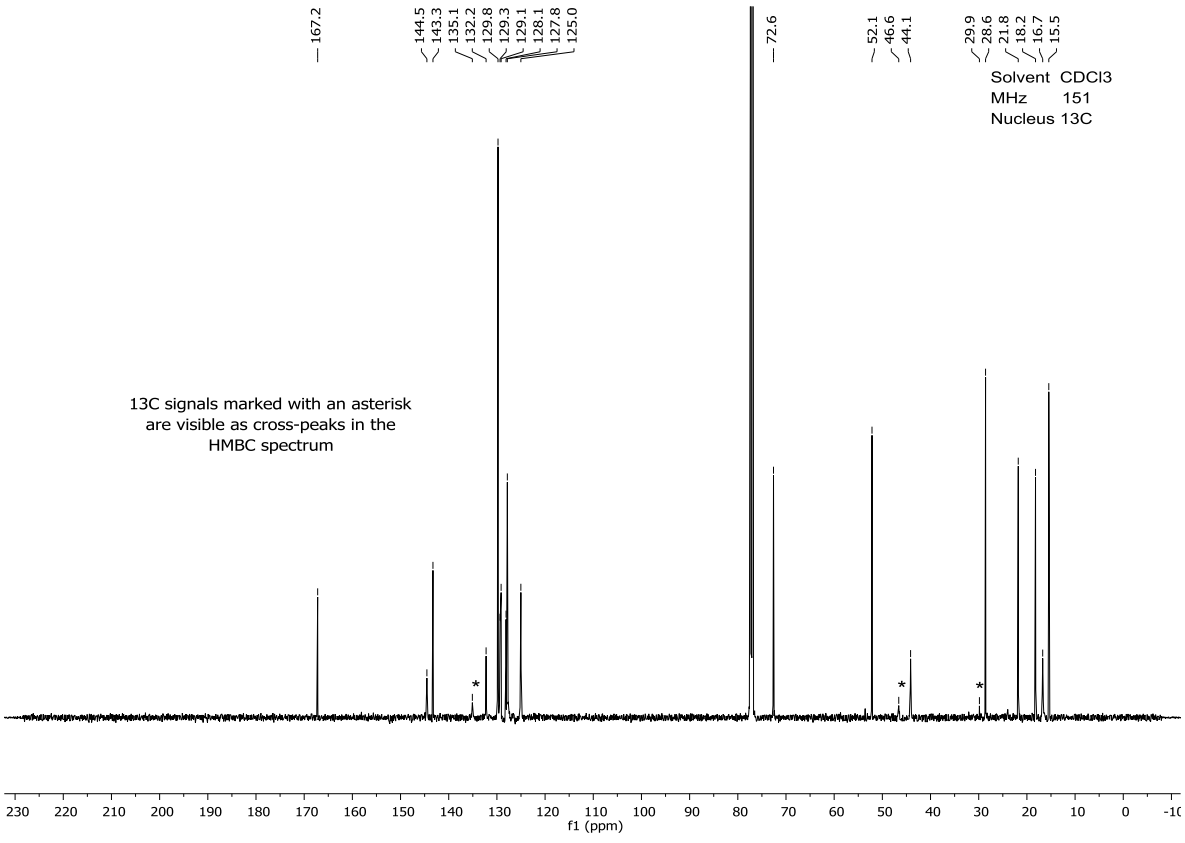

199.8
166.7
144.5
141.5
136.1
133.2
131.1
130.3
129.9
128.8
128.7
128.5
128.5
128.4
128.3
128.1
128.0
127.7
127.7
127.3
127.1
125.9
56.2
51.6
46.2
28.7
18.1
18.0
14.0
Solvent C6D6
MHz 201
Nucleus 13C
f1 (ppm)

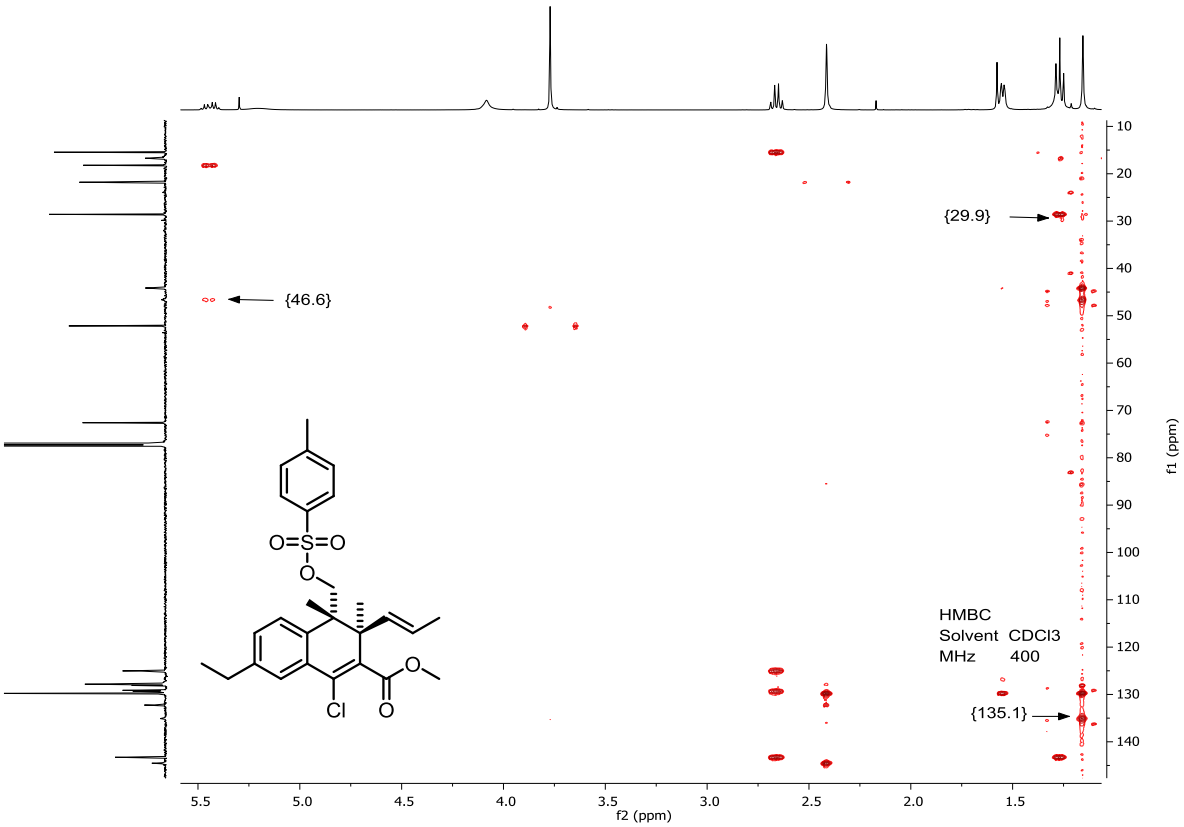

HO
Me
Me
Cl
O
O
Solvent CDCl3
MHz 400
Nucleus 1H
1.00
0.96
1.06
1.08
0.79
1.05
3.07
0.88
2.11
3.09
3.09
3.82
3.23
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

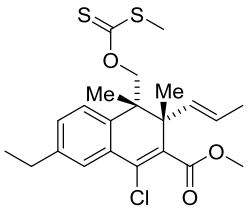

167.6
143.3
135.9
131.0
129.9
129.2
127.9
127.4
126.0
125.4
66.0
52.2
46.5
45.8
29.9
28.6
18.3
16.4
16.4
15.5
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HO
Me
Me
O
Cl
O
{16.4}
{127.9}
{127.4}
HSQC
Solvent CDCl3
MHz 400
f1 (ppm)
f2 (ppm)

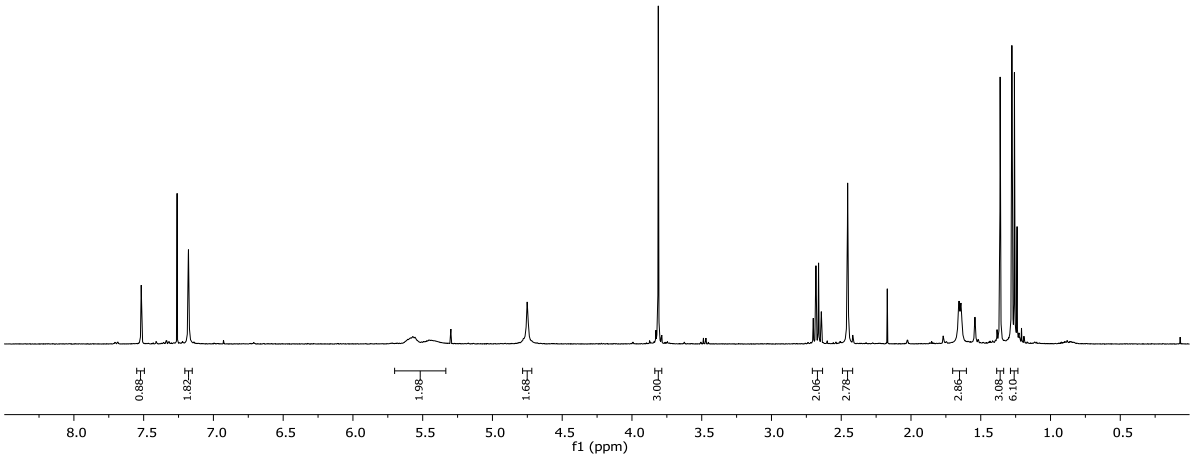

Solvent CDCl3
MHz 400
Nucleus 1H
O=S=O
O
Cl
O
O
1.41
1.01
3.95
1.11
0.85
2.01
3.00
2.11
3.18
3.04
6.10
3.14
f1 (ppm)

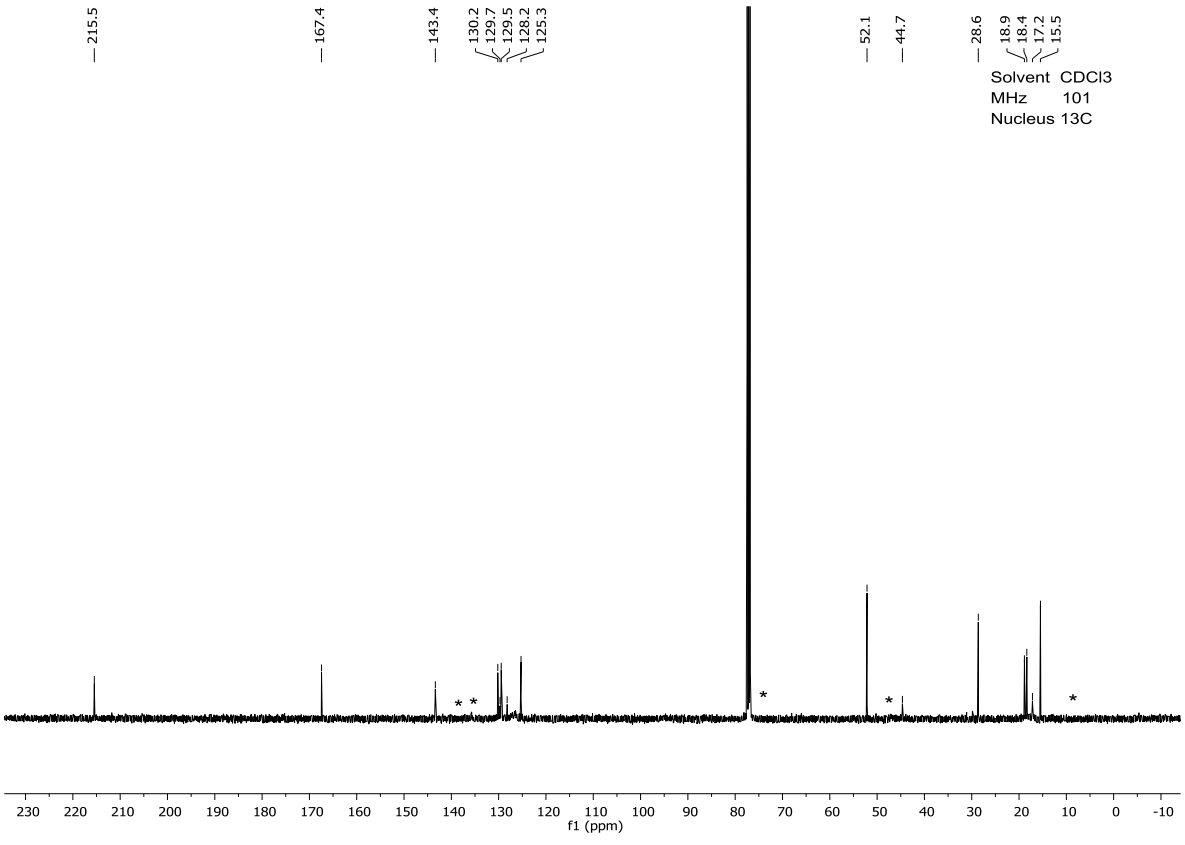

167.2
144.5
143.3
135.1
132.2
129.8
129.3
129.1
128.1
127.8
125.0
72.6
52.1
46.6
44.1
29.9
28.6
21.8
18.2
16.7
15.5
Solvent CDCl3
MHz 151
Nucleus 13C
13C signals marked with an asterisk
are visible as cross-peaks in the
HMBC spectrum
*
*
*
f1 (ppm)

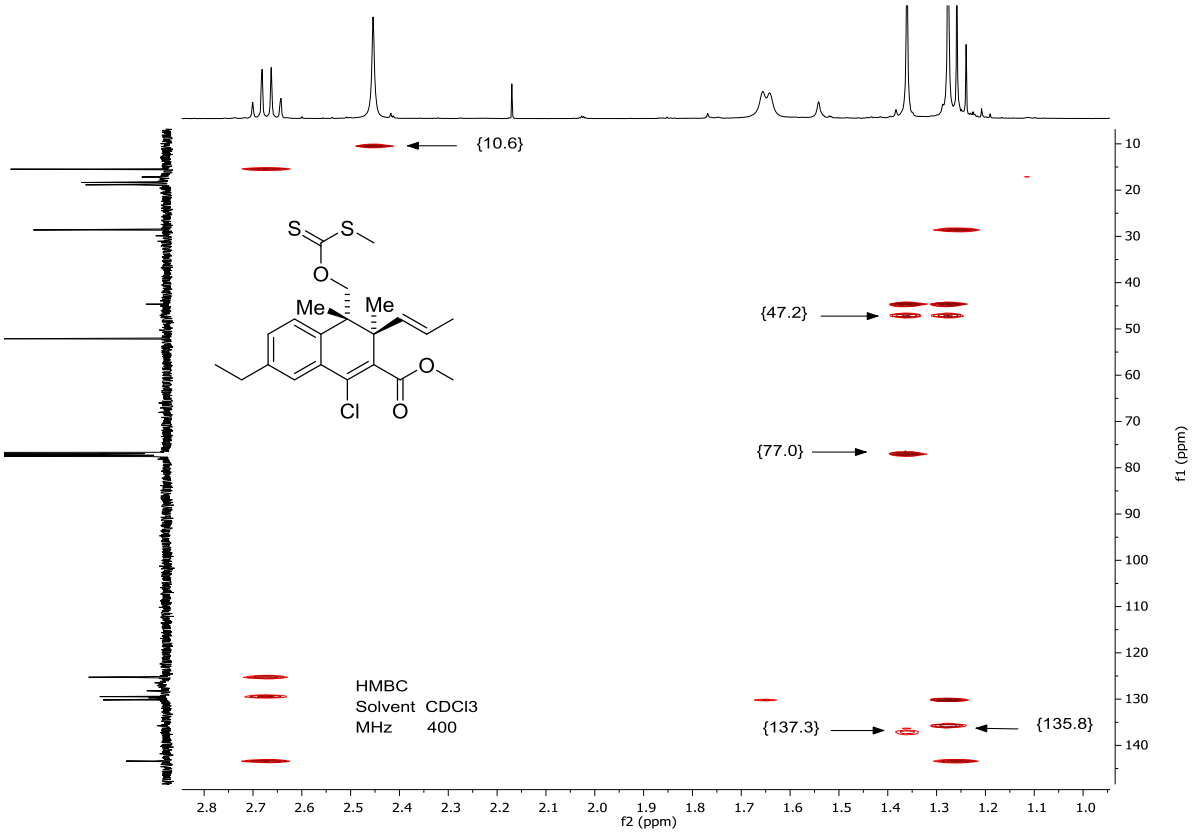

{29.9}
{46.6}
{135.1}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
10
20
30
40
50
60
70
80
90
100
110
120
130
140
O=S=O
O
Cl
O
O

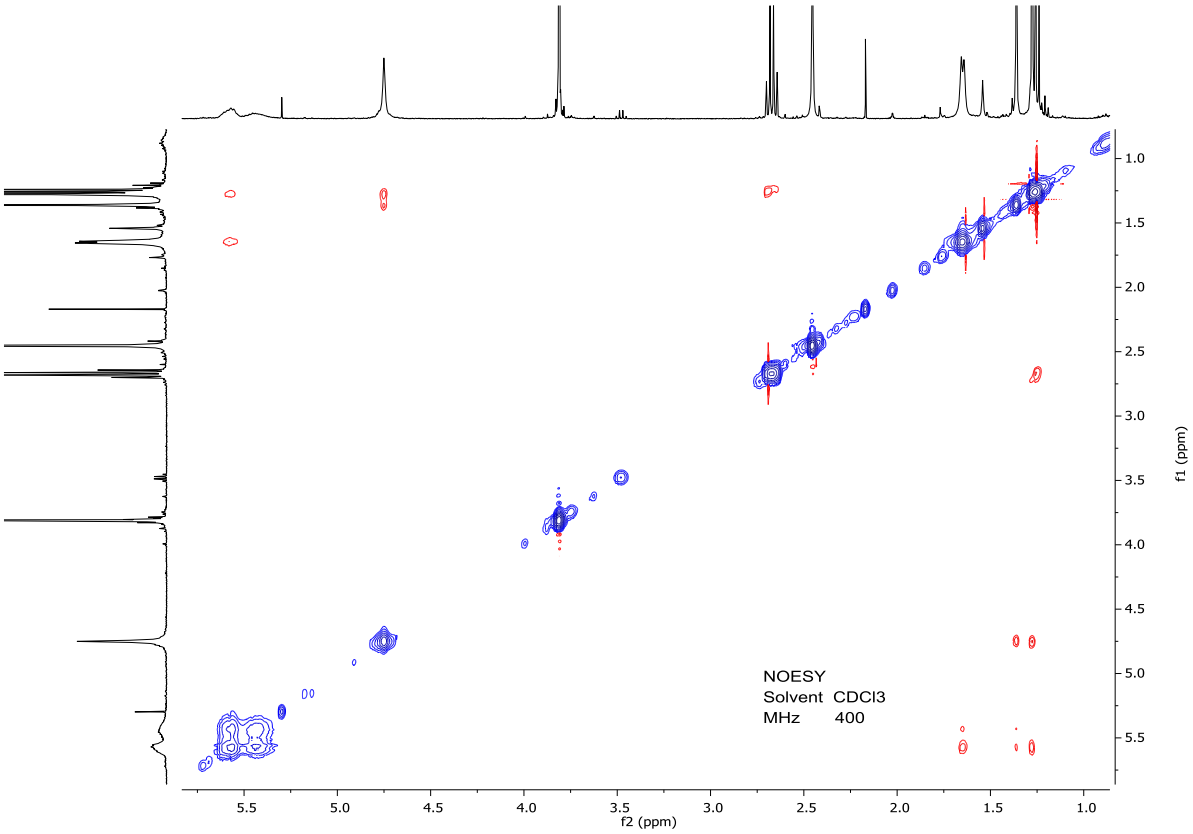


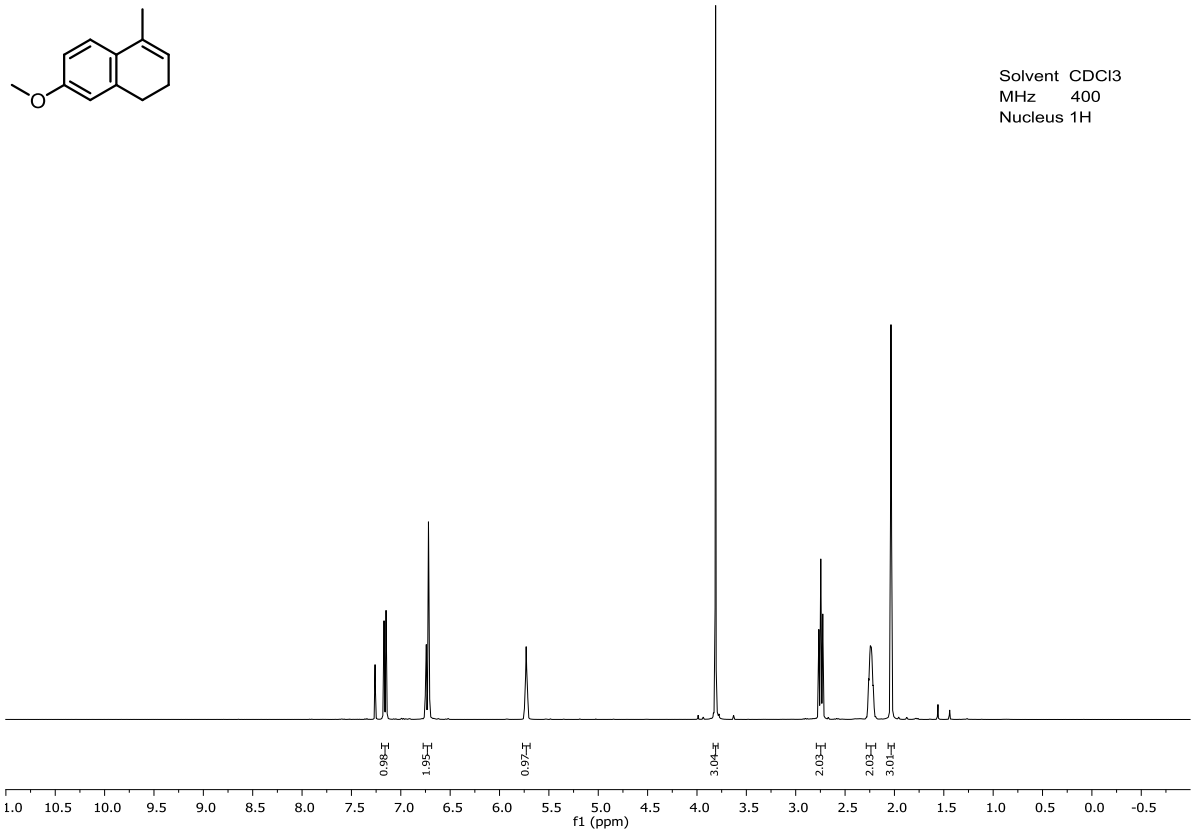
Solvent CDCl3
MHz 400
Nucleus 1H

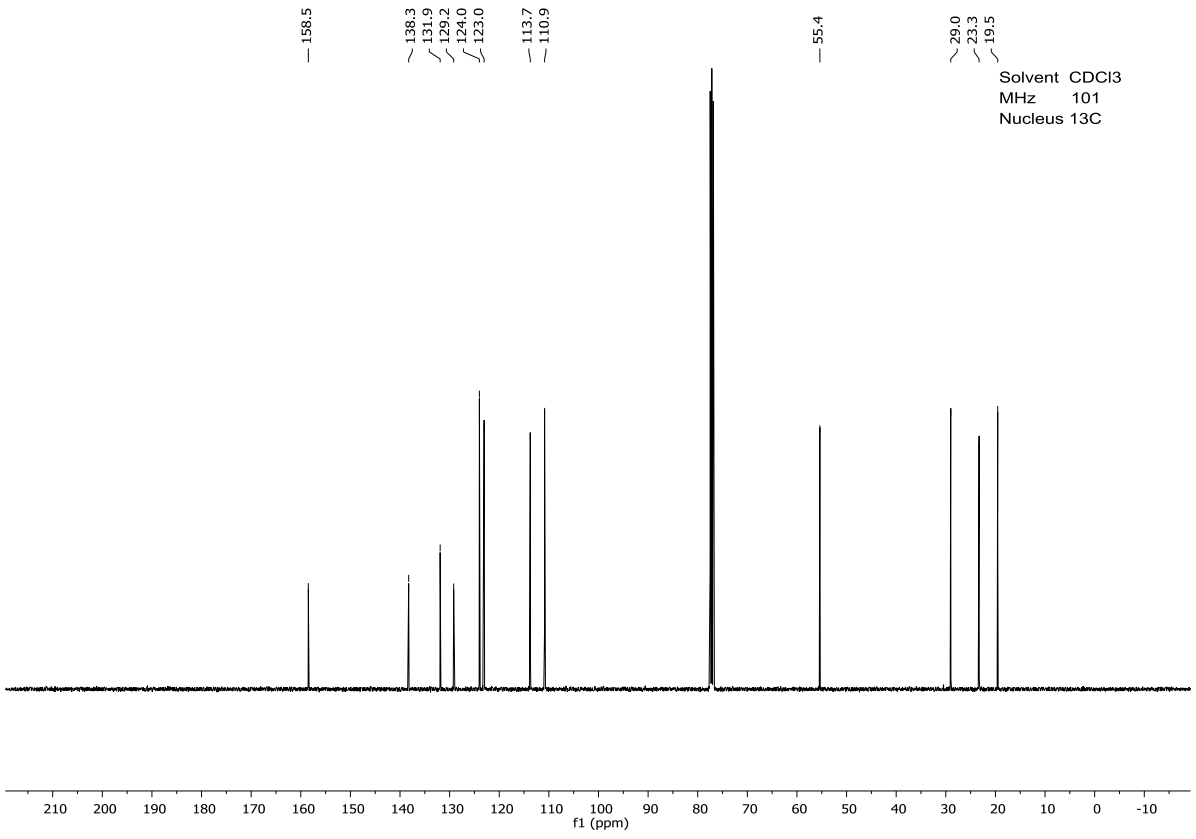


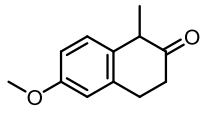



{10.6}
{47.2}
{77.0}
{137.3}
{135.8}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

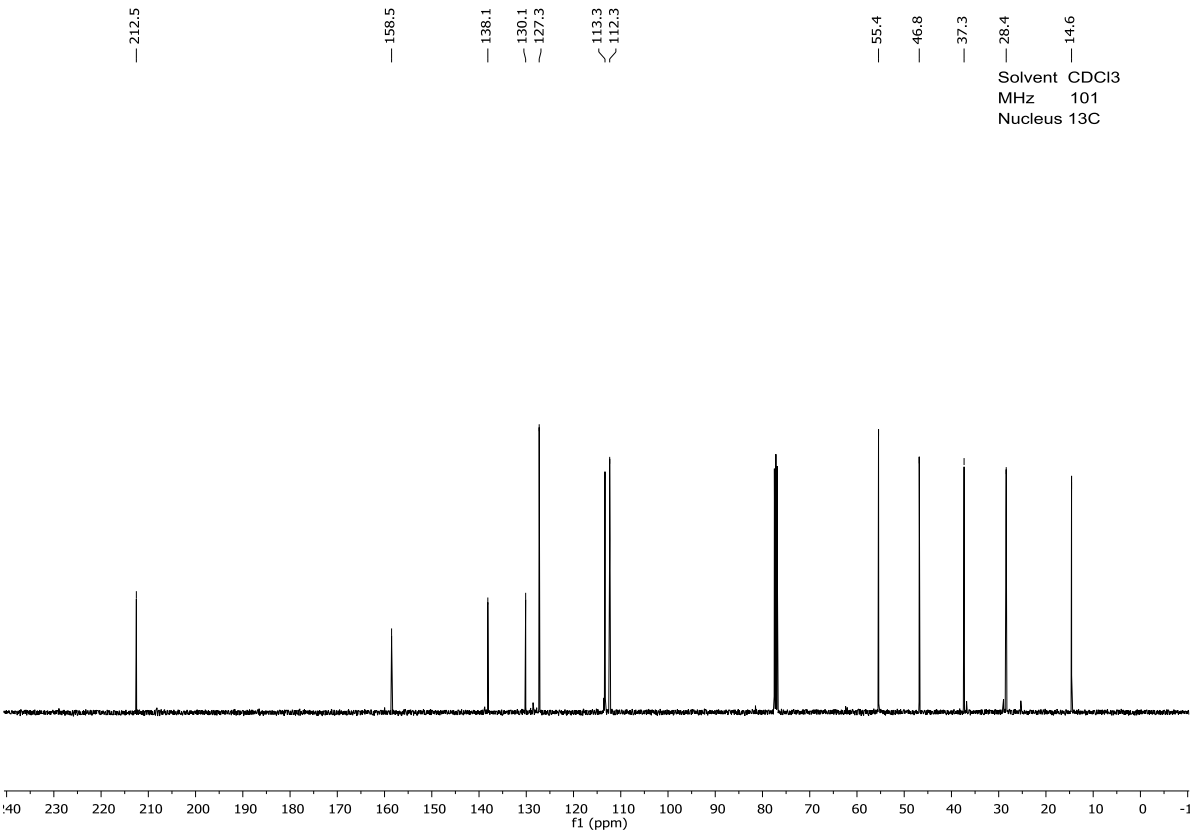

NOESY
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

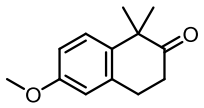

Solvent CDCl3
MHz 400
Nucleus 1H
0.98
1.95
0.97
3.04
2.03
2.03
3.01
f1 (ppm)

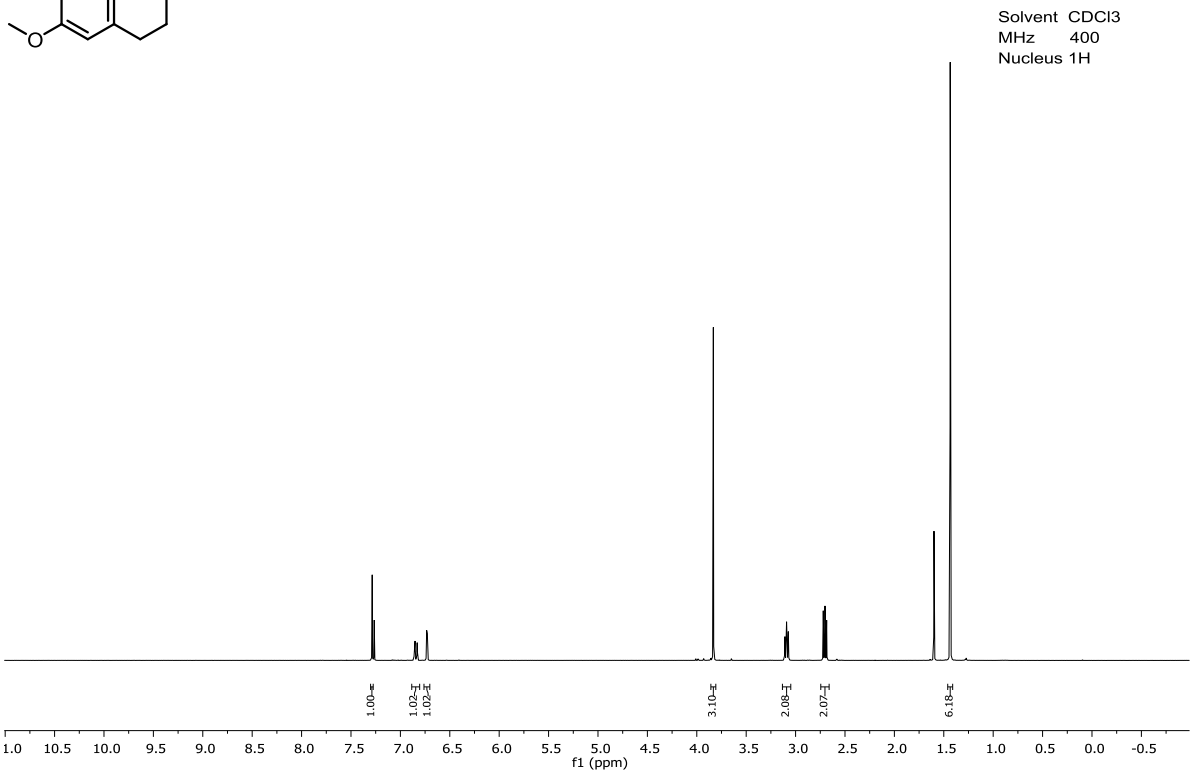

158.5
138.3
131.9
129.2
124.0
123.0
113.7
110.9
55.4
29.0
23.3
19.5
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

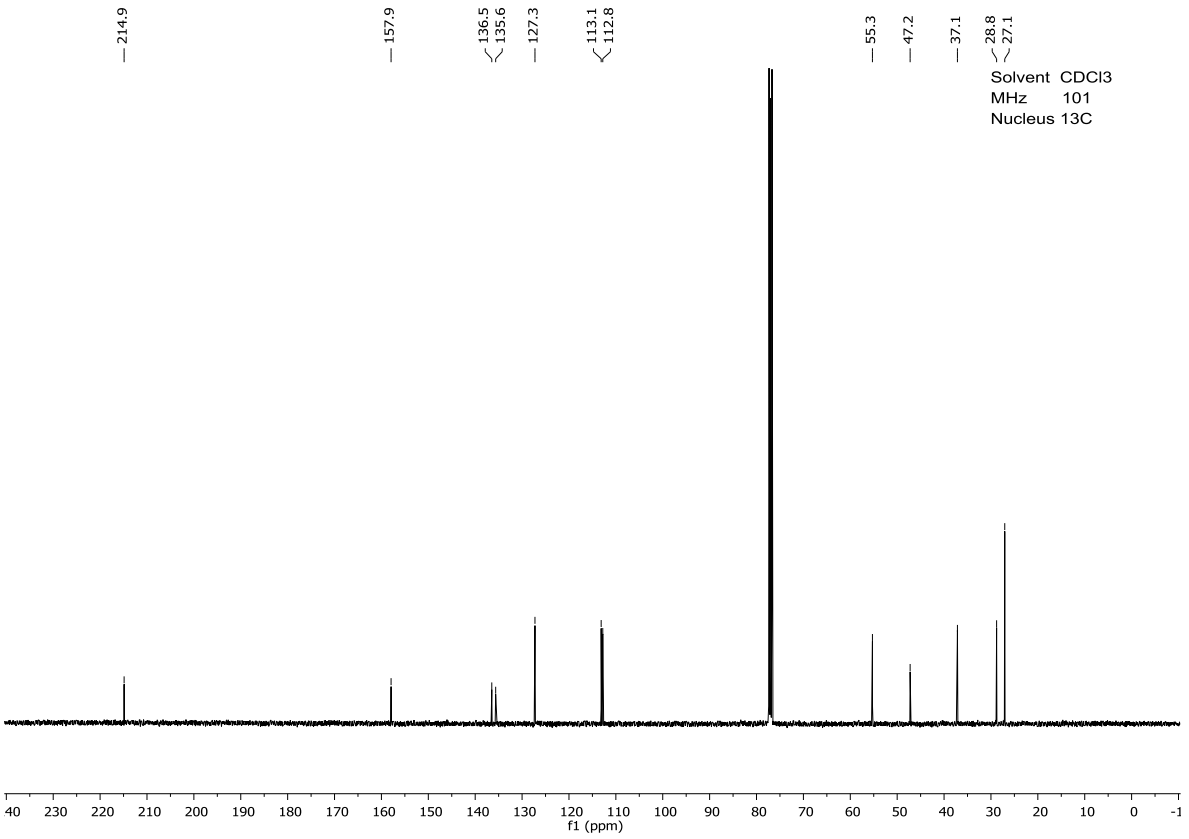


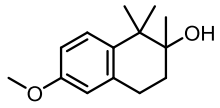
Solvent CDCl3
MHz 400
Nucleus 1H
0.96
1.87
3.16
0.94
2.08
1.02
0.99
2.97
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


212.5
158.5
138.1
130.1
127.3
113.3
112.3
55.4
46.8
37.3
28.4
14.6
Solvent CDCl3
MHz 101
Nucleus 13C
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

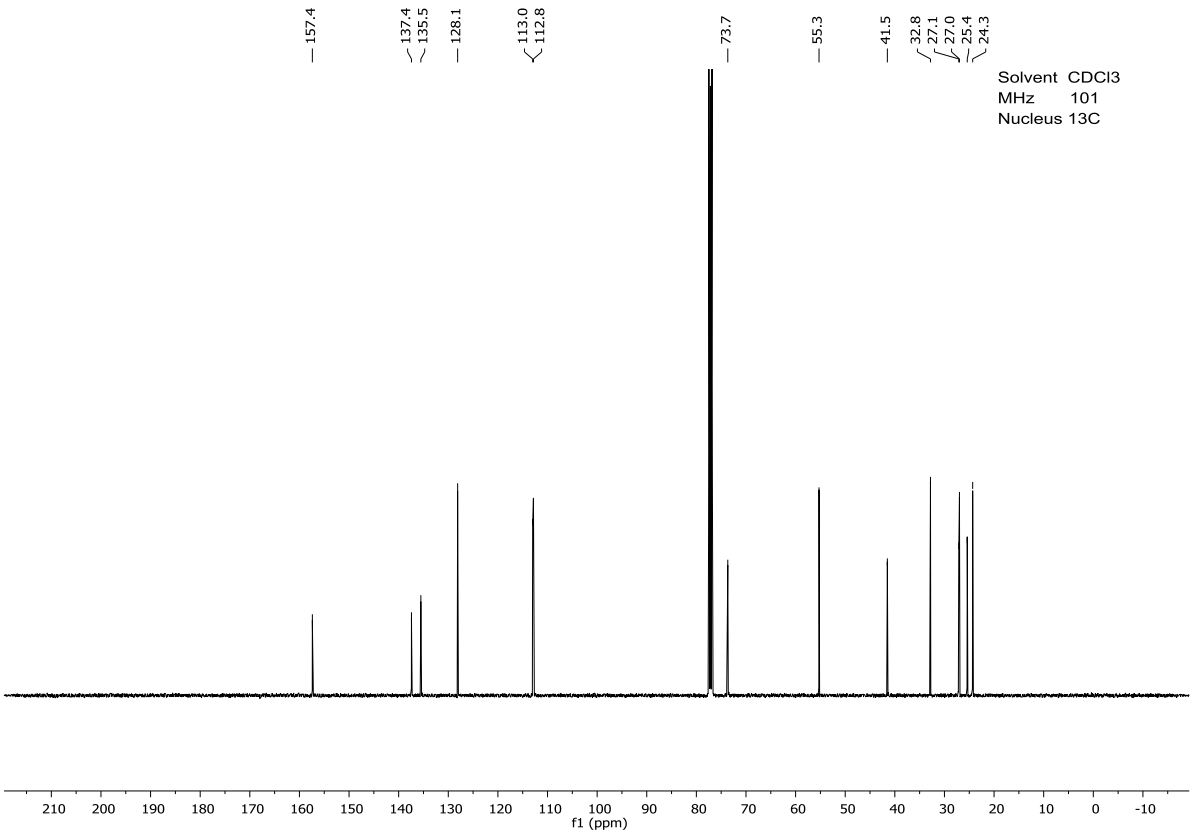


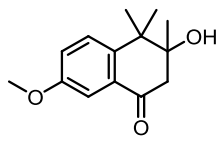

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.02
1.02
3.10
2.08
2.07
6.18
f1 (ppm)


214.9
157.9
136.5
135.6
127.3
113.1
112.8
55.3
47.2
37.1
28.8
27.1
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

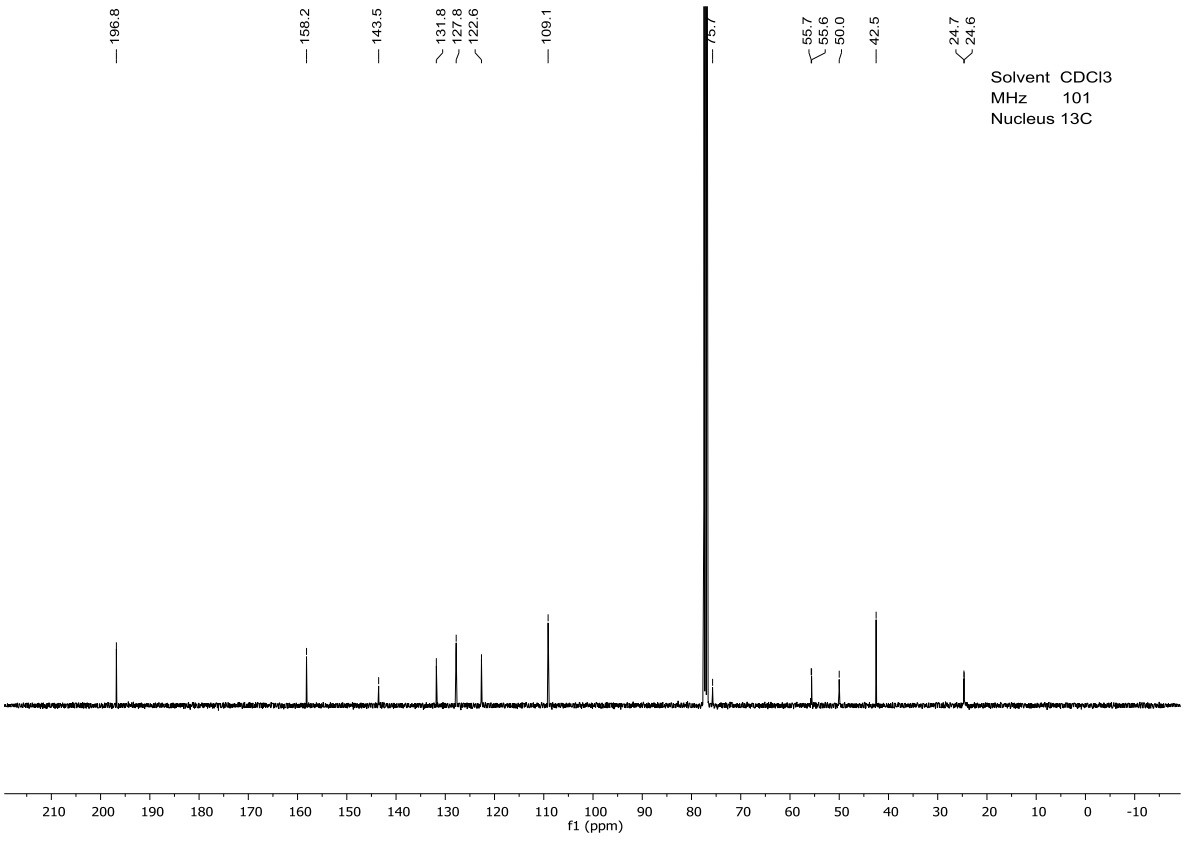

OH
O

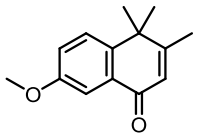
Solvent CDCl3
MHz 400
Nucleus 1H
1.17
0.95
0.95
2.93
1.00
1.01
2.00
3.02
5.96
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


157.4
137.4
135.5
128.1
113.0
112.8
73.7
55.3
41.5
32.8
27.1
27.0
25.4
24.3
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

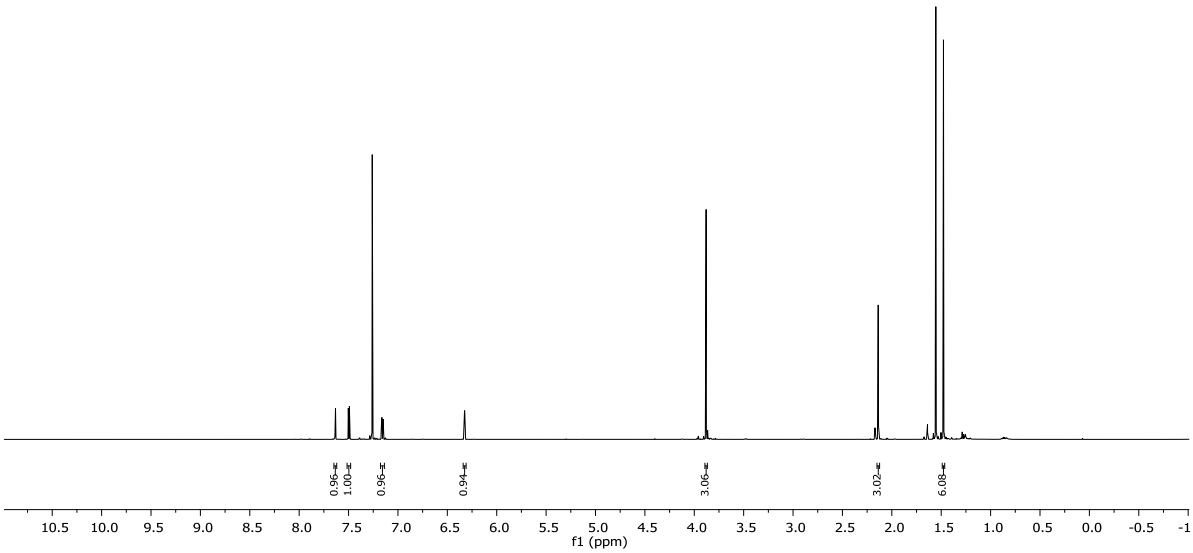

OH
O
O

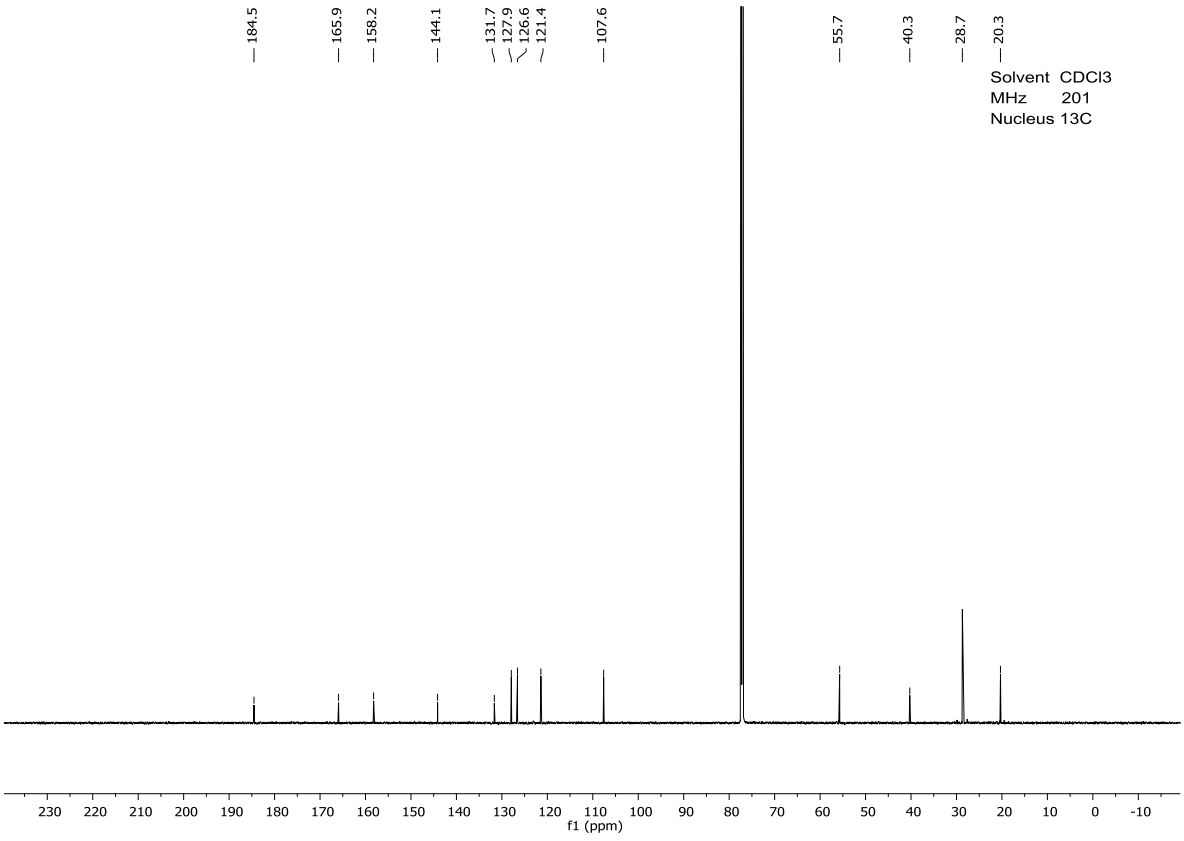
Solvent CDCl3
MHz 400
Nucleus 1H
0.97
1.00
0.99
3.00
2.19
3.10
3.19
3.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

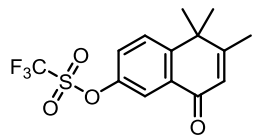

196.8
158.2
143.5
131.8
127.8
122.6
109.1
75.7
55.7
55.6
50.0
42.5
24.7
24.6
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



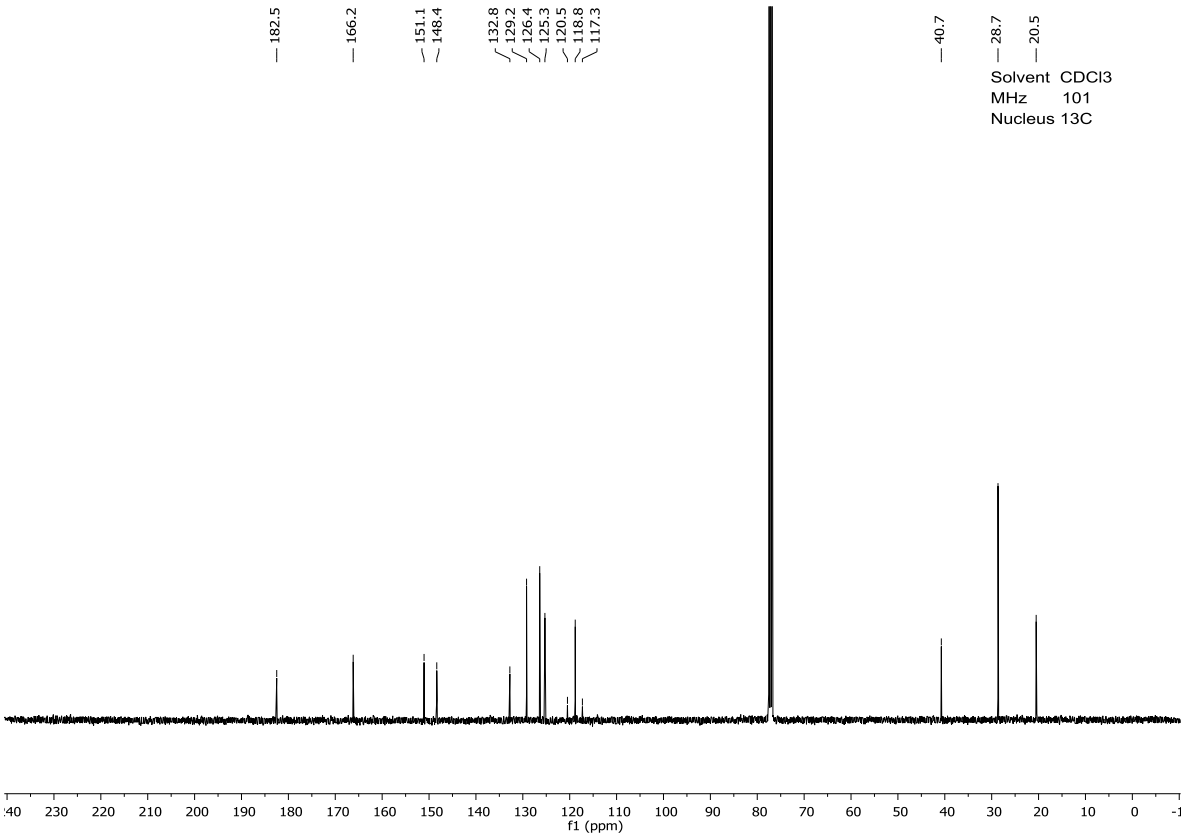
Solvent CDCl3
MHz 800
Nucleus 1H

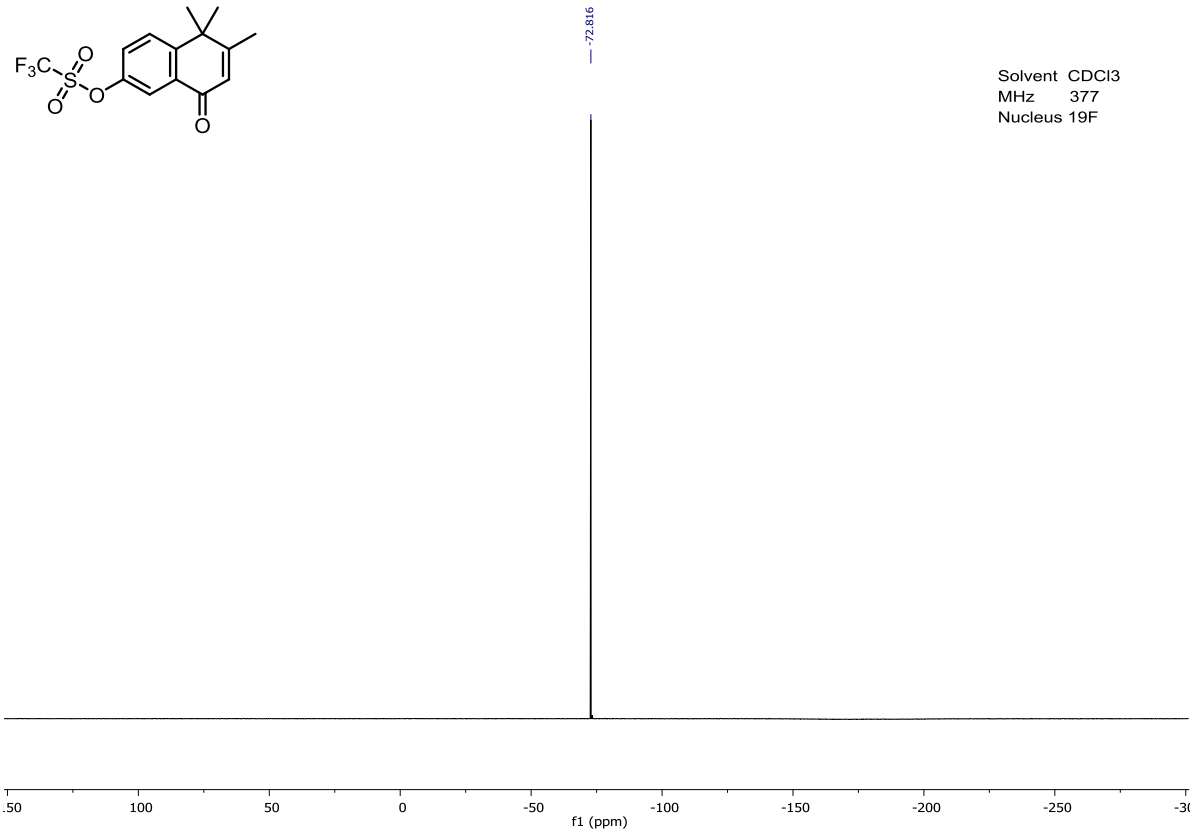


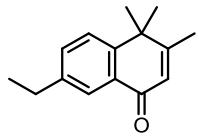



F3C
S
O
O
O
O

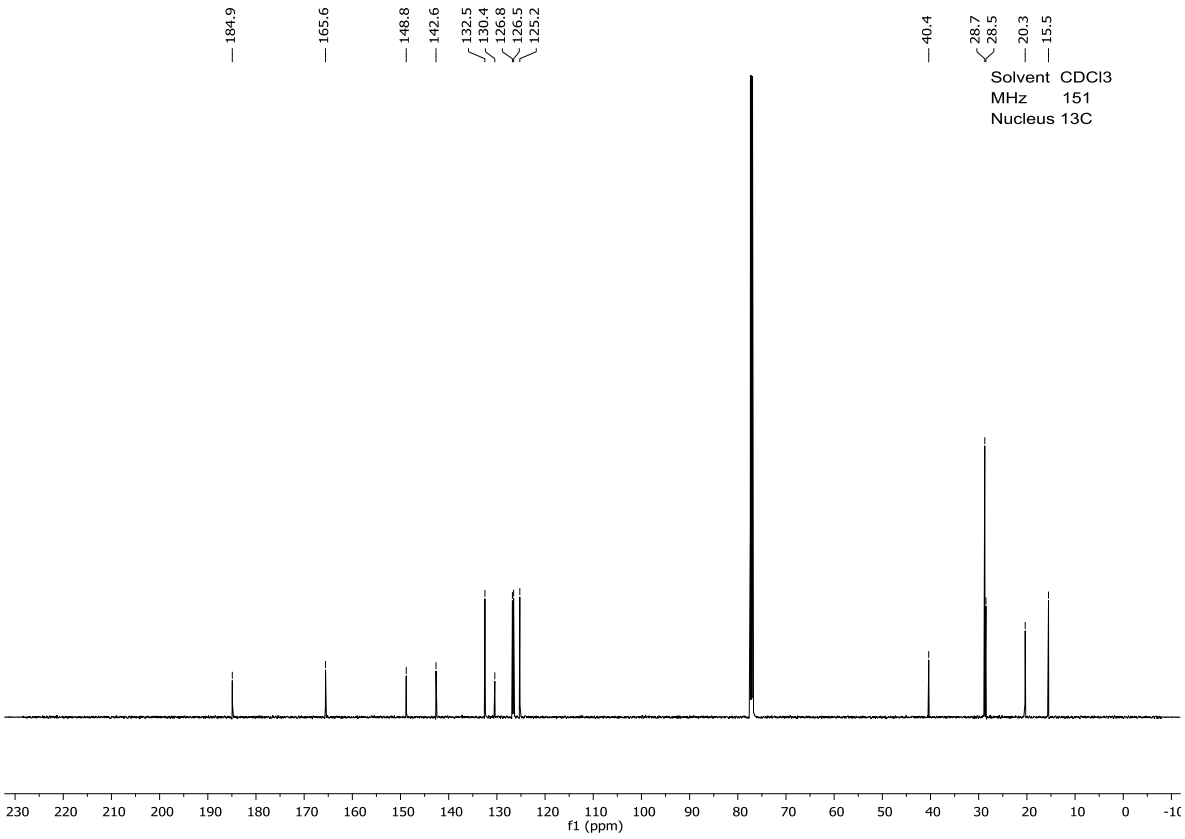
Solvent CDCl3
MHz 400
Nucleus 1H
0.94
1.05
1.01
0.93
3.01
6.06
f1 (ppm)

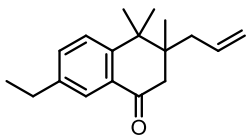

182.5
166.2
151.1
148.4
132.8
129.2
126.4
125.3
120.5
118.8
117.3
40.7
28.7
20.5
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


F3C
S
O
O
O
O
-72.816
Solvent CDCl3
MHz 377
Nucleus 19F
.50
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)

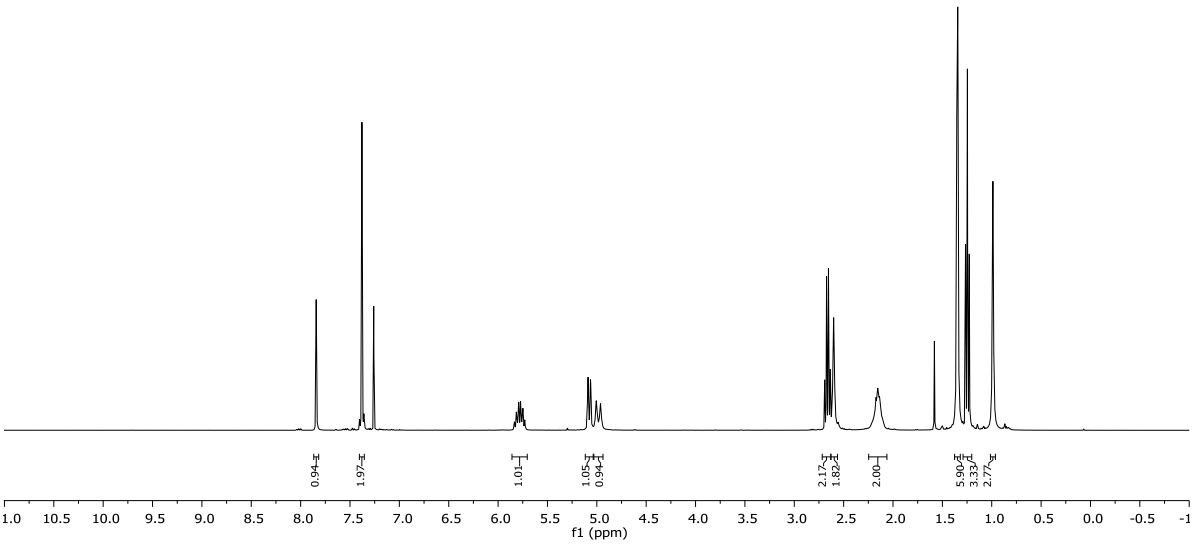


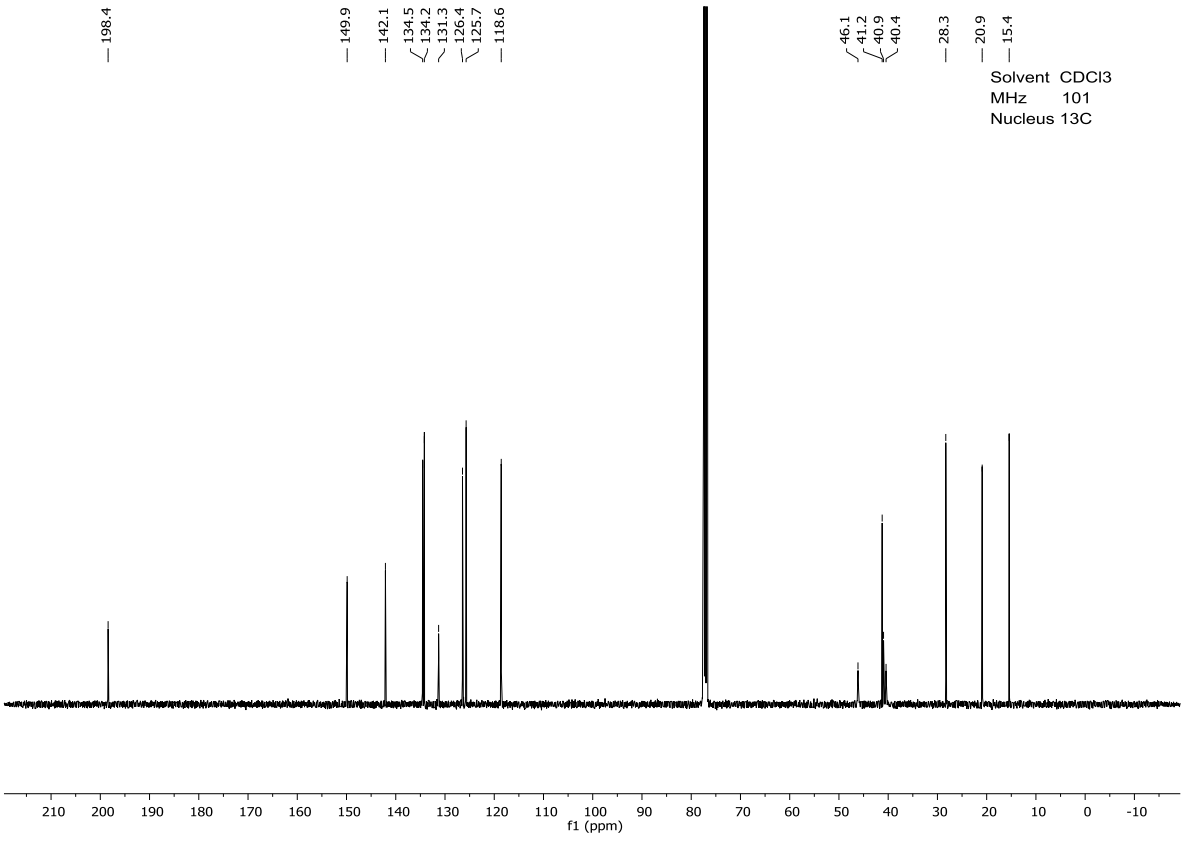
Solvent CDCl3
MHz 599
Nucleus 1H
1.00
0.96
1.03
0.87
2.10
2.96
6.07
3.37
f1 (ppm)

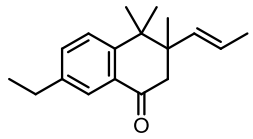

184.9
165.6
148.8
142.6
132.5
130.4
126.8
126.5
125.2
40.4
28.7
28.5
20.3
15.5
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)



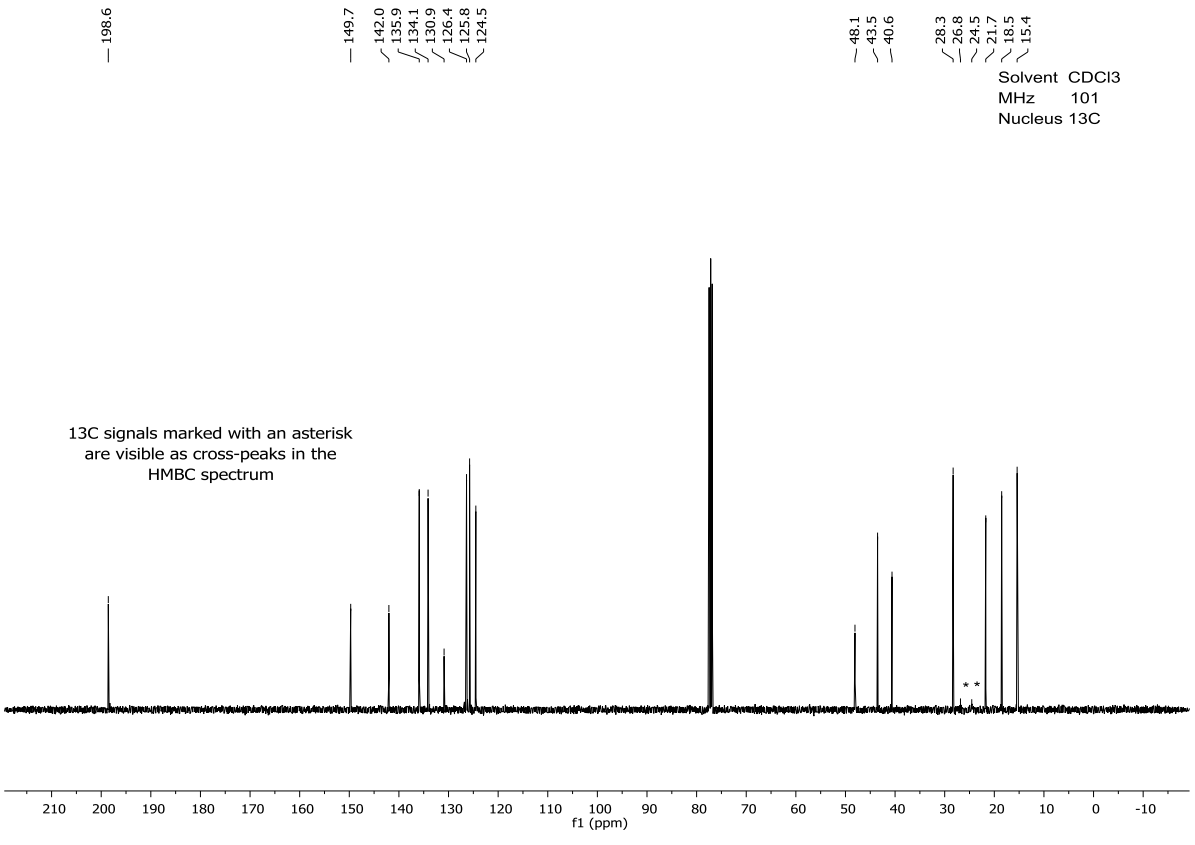
Solvent CDCl3
MHz 400
Nucleus 1H

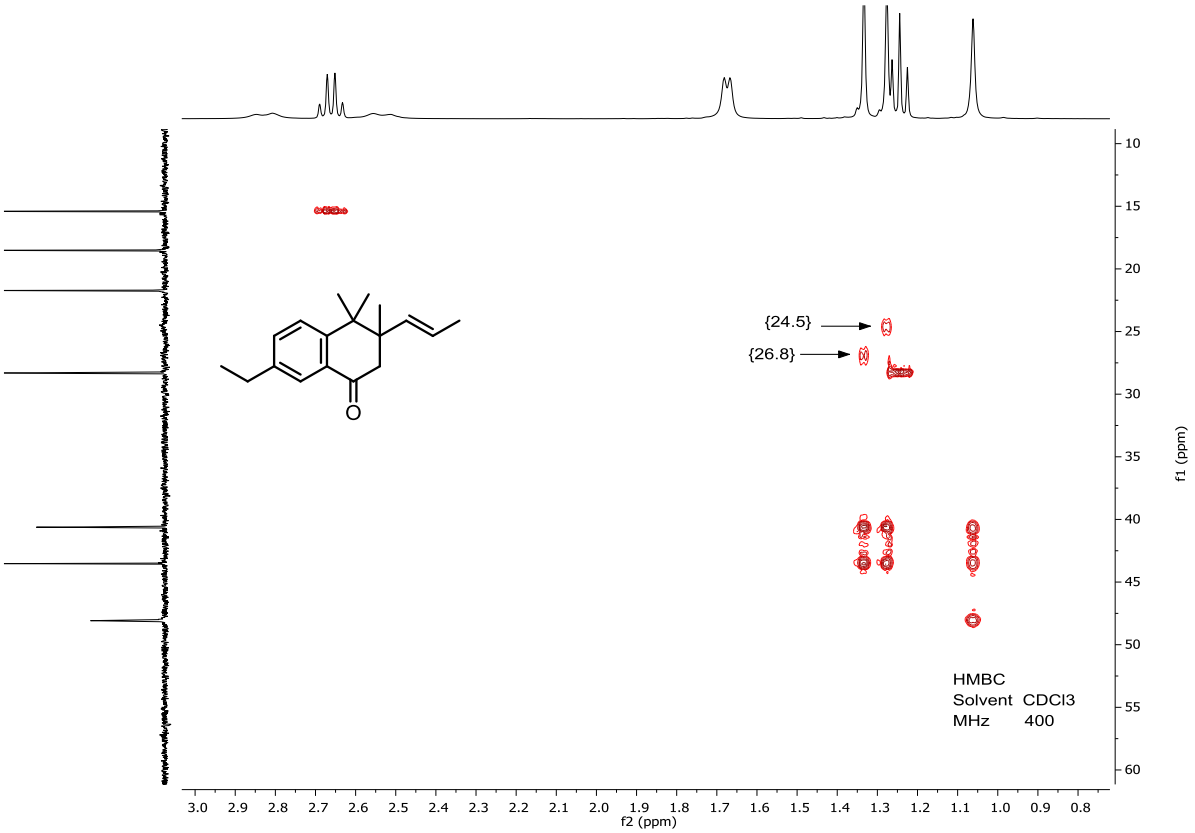


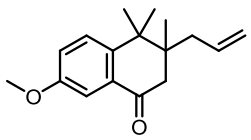




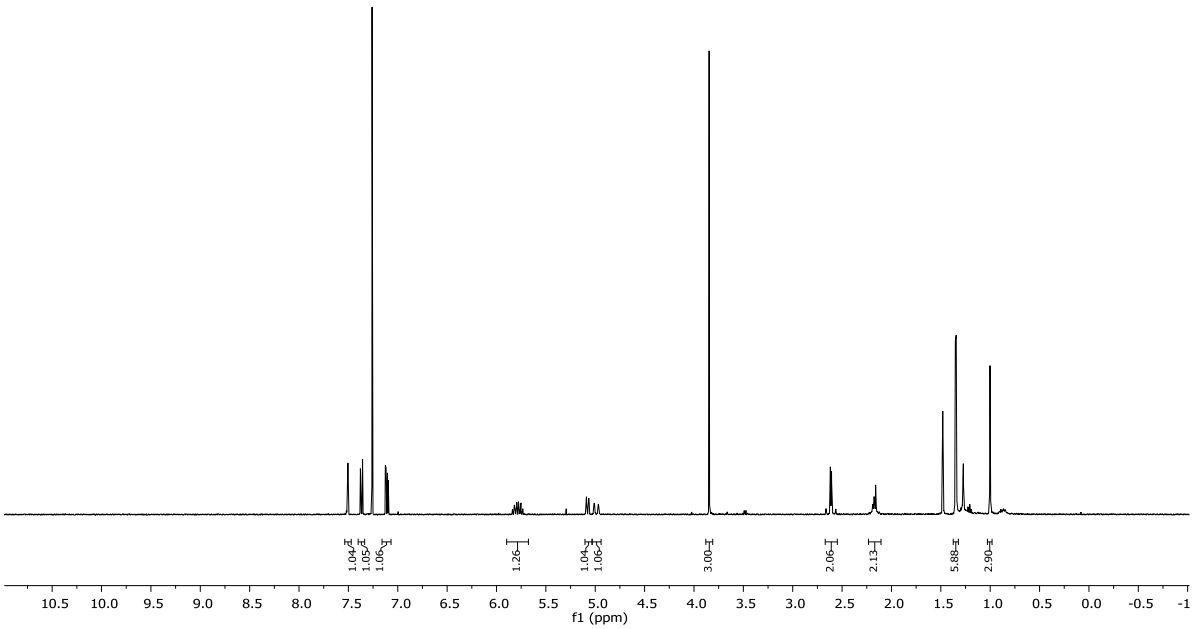
Solvent CDCl3
MHz 400
Nucleus 1H
0.96
2.05
0.96
1.03
0.90
2.15
0.89
2.90
3.22
6.26
2.92
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

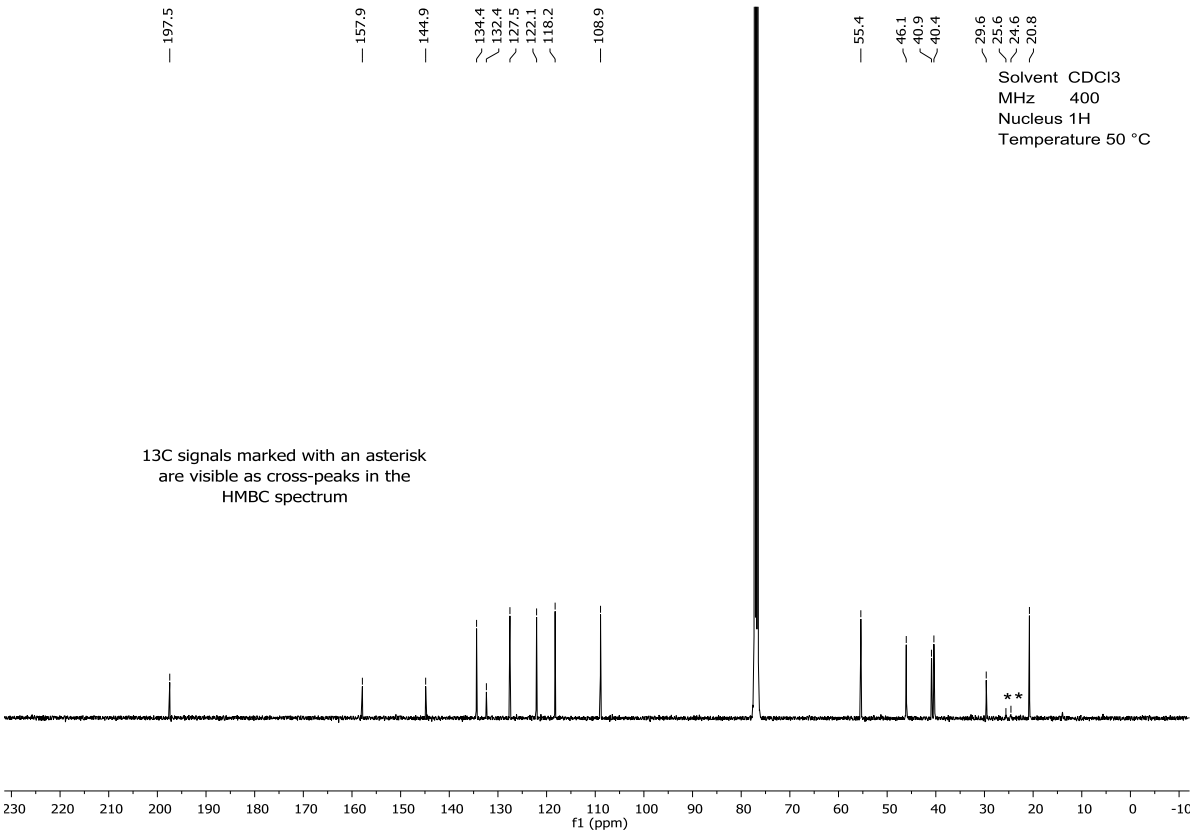

198.6
149.7
142.0
135.9
134.1
130.9
126.4
125.8
124.5
48.1
43.5
40.6
28.3
26.8
24.5
21.7
18.5
15.4
Solvent CDCl3
MHz 101
Nucleus 13C
13C signals marked with an asterisk
are visible as cross-peaks in the
HMBC spectrum
* *
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

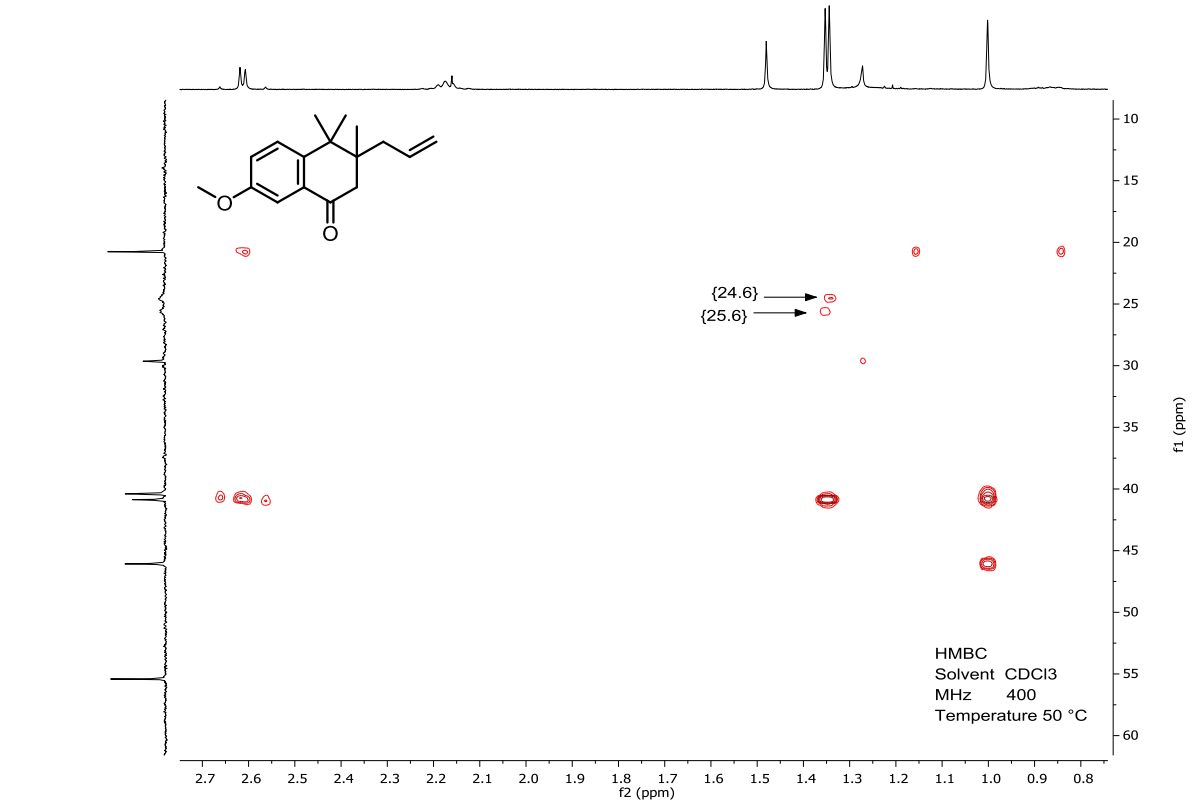

{24.5}
{26.8}
HMBC
Solvent CDCl3
MHz 400
f1 (ppm)
f2 (ppm)
3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8
10 15 20 25 30 35 40 45 50 55 60
O

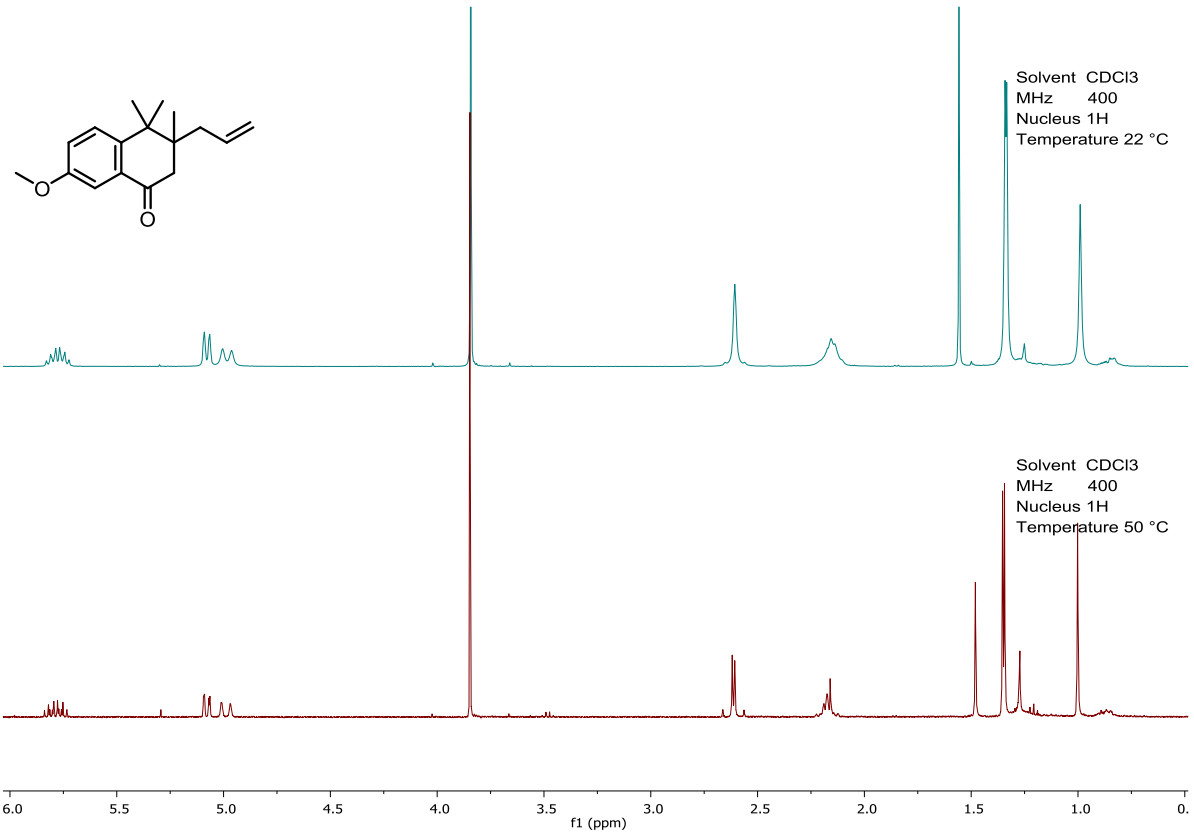


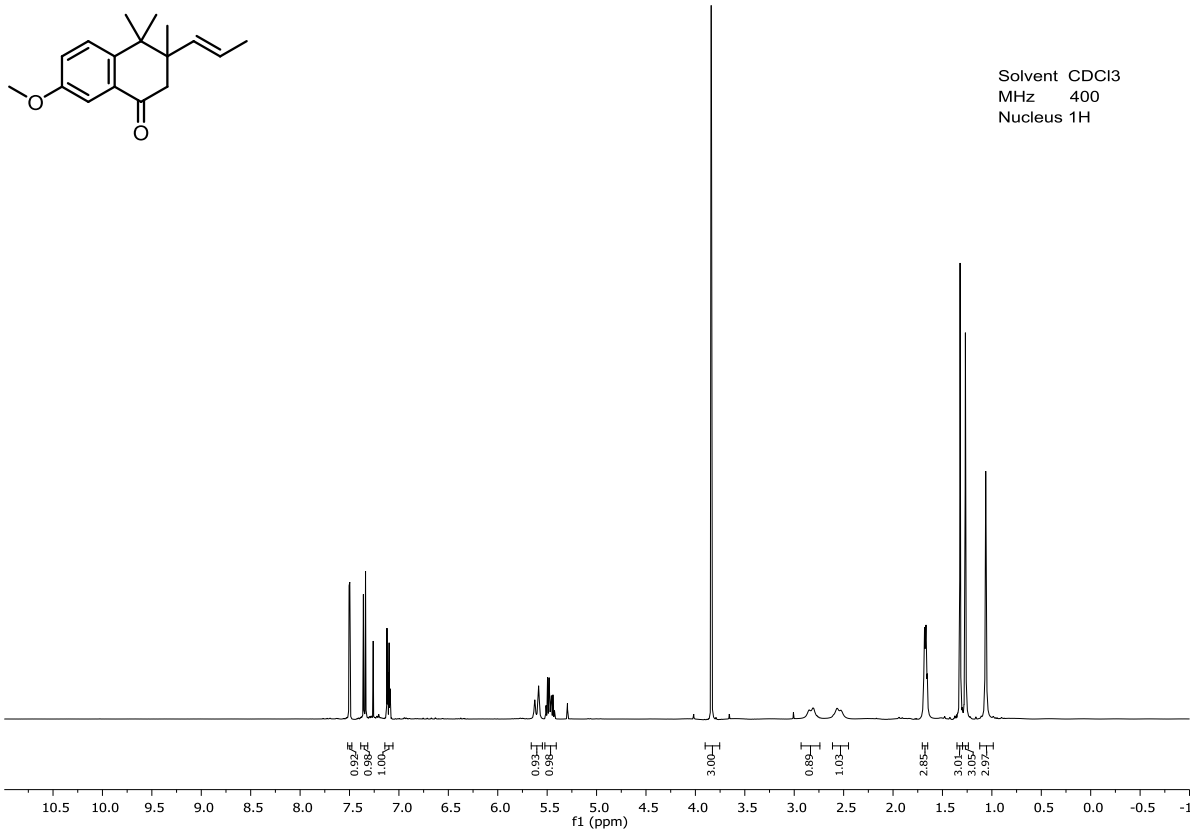
Solvent CDCl3
MHz 400
Nucleus 1H
Temperature 50°C

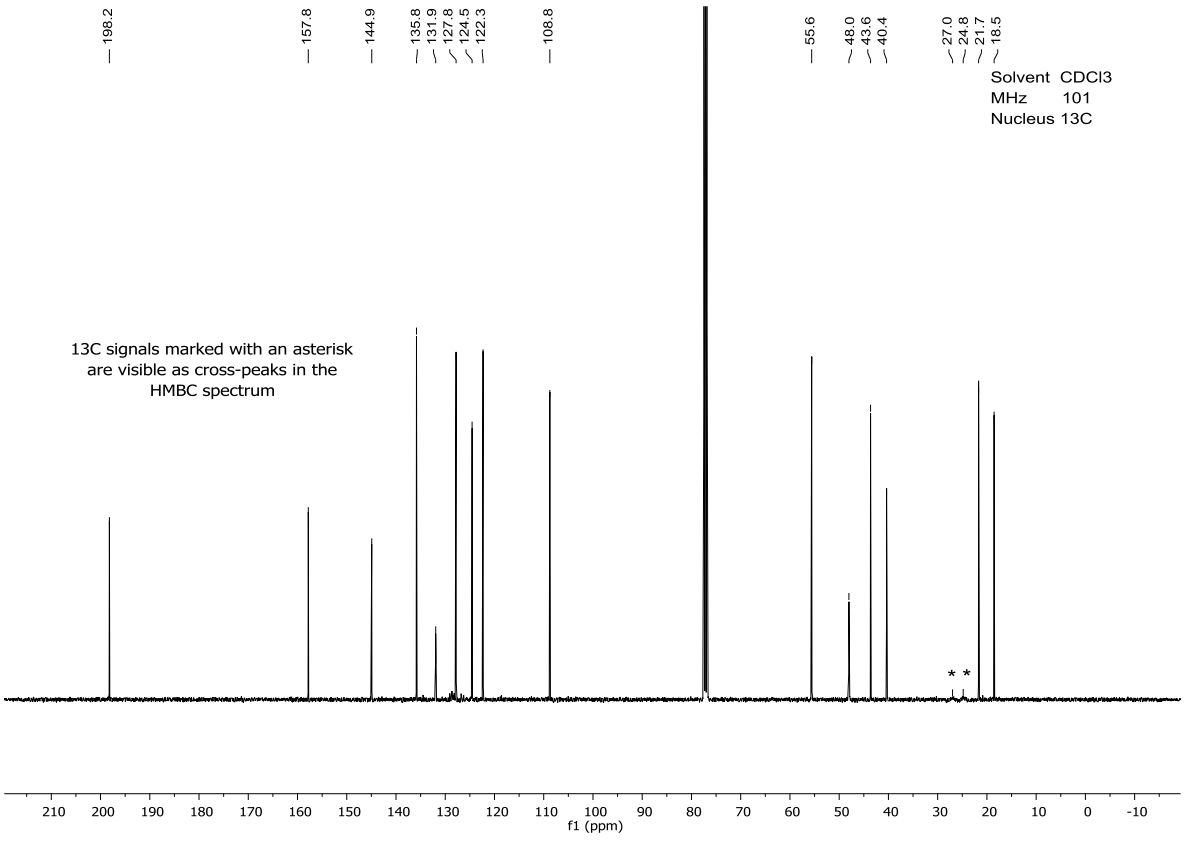


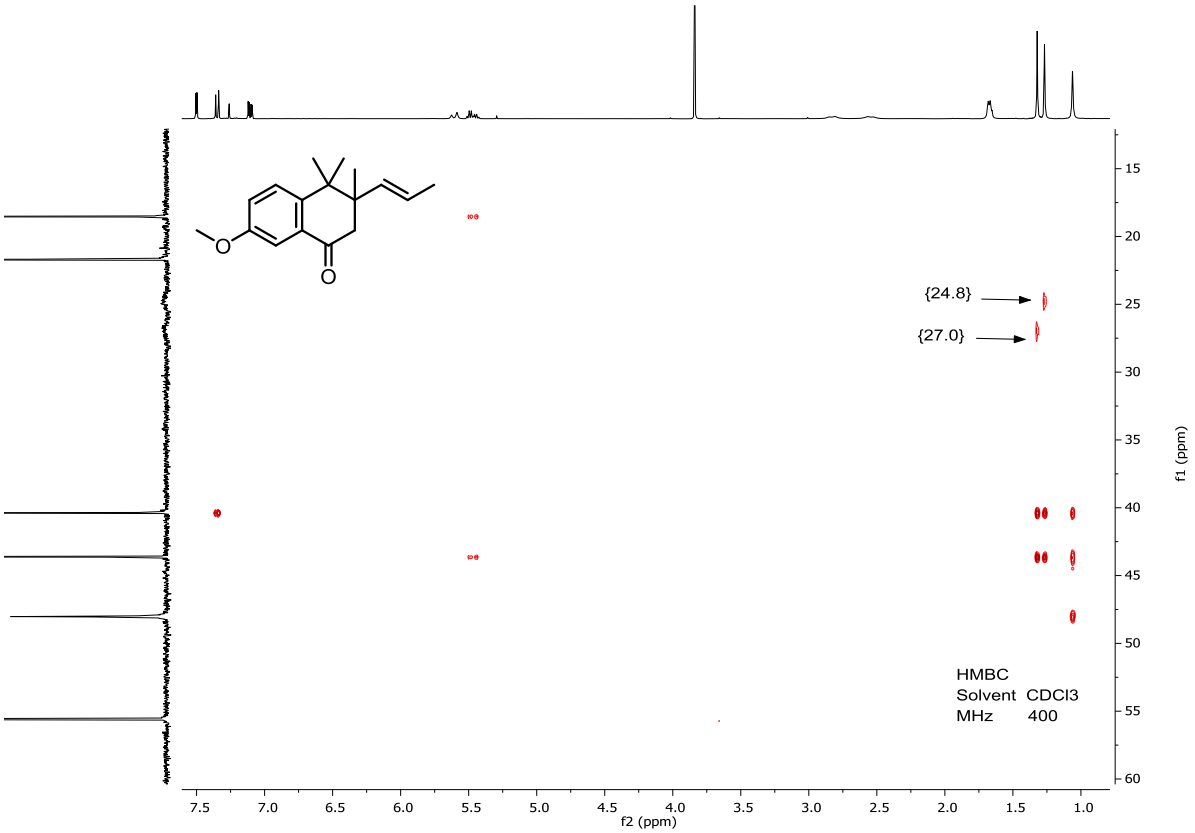


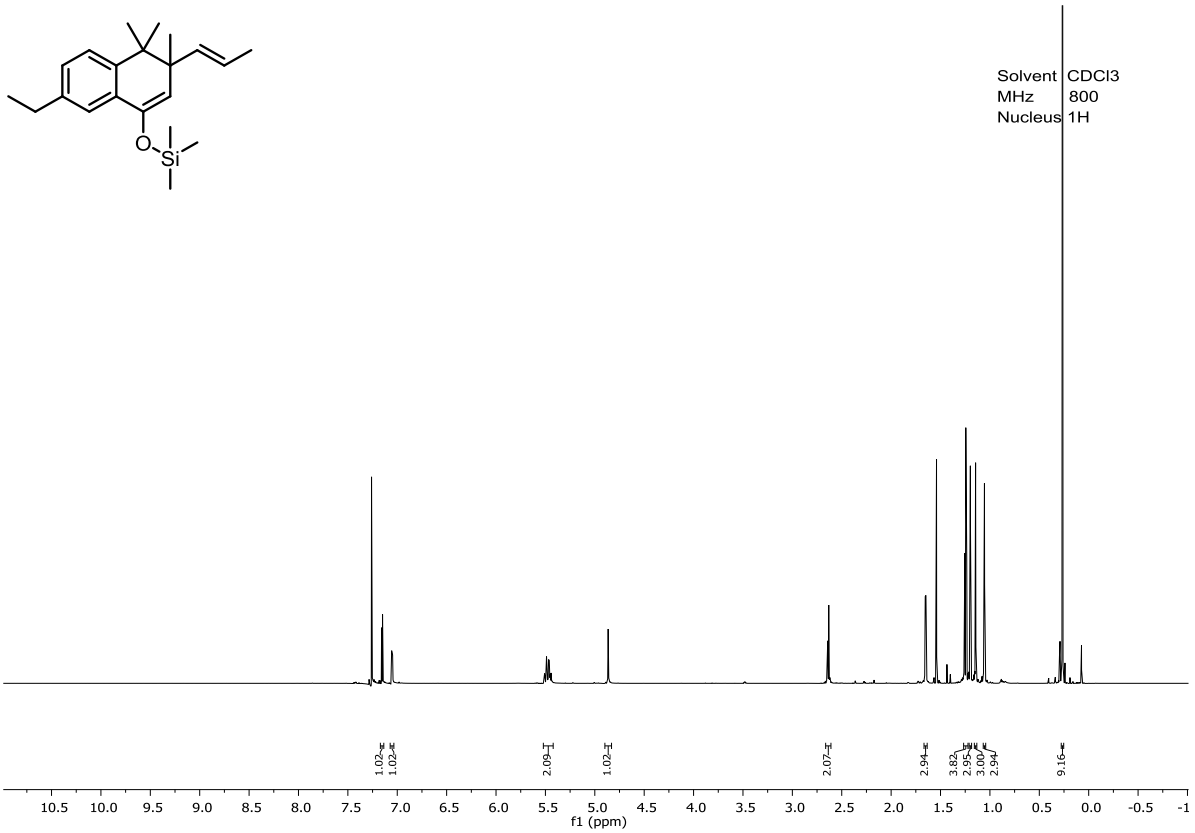

{24.6}
{25.6}
HMBC
Solvent CDCl3
MHz 400
Temperature 50 °C
f2 (ppm)
f1 (ppm)

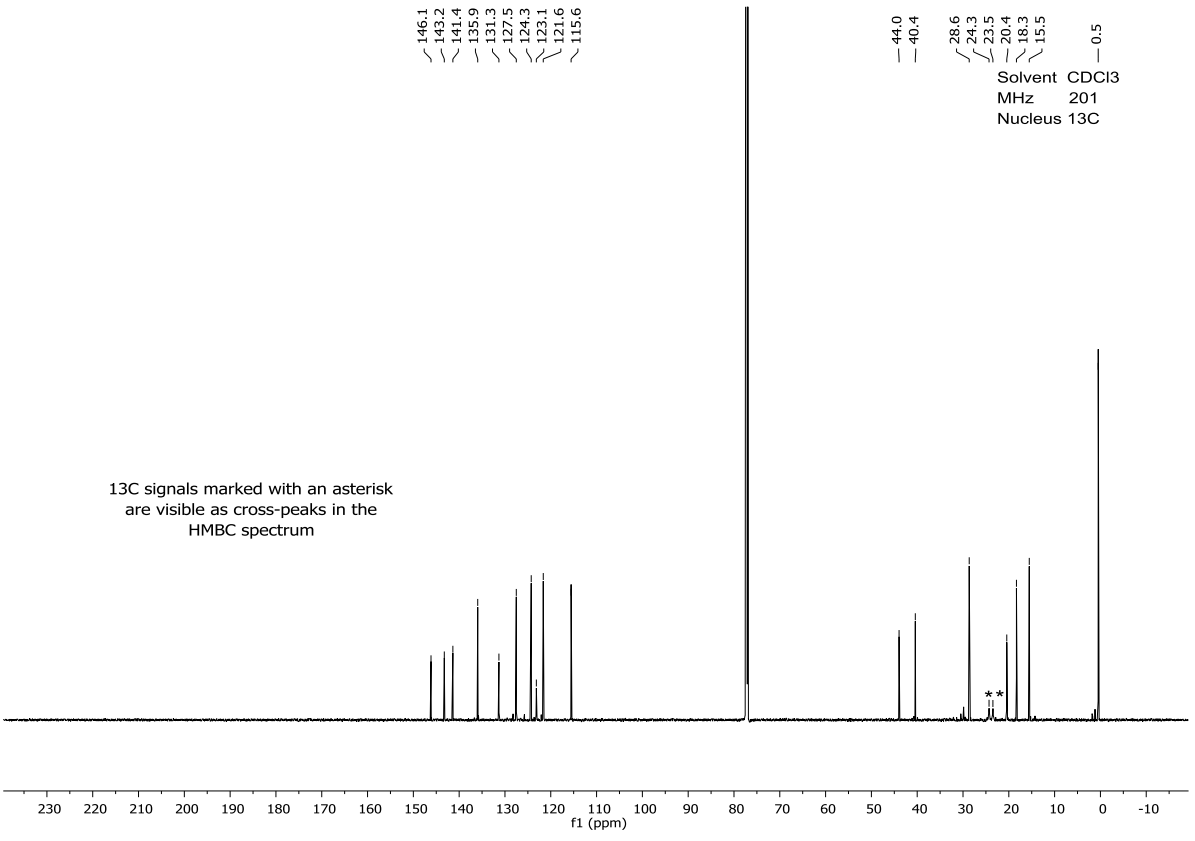

Solvent CDCl3
MHz 400
Nucleus 1H
Temperature 22 °C
Solvent CDCl3
MHz 400
Nucleus 1H
Temperature 50 °C
f1 (ppm)

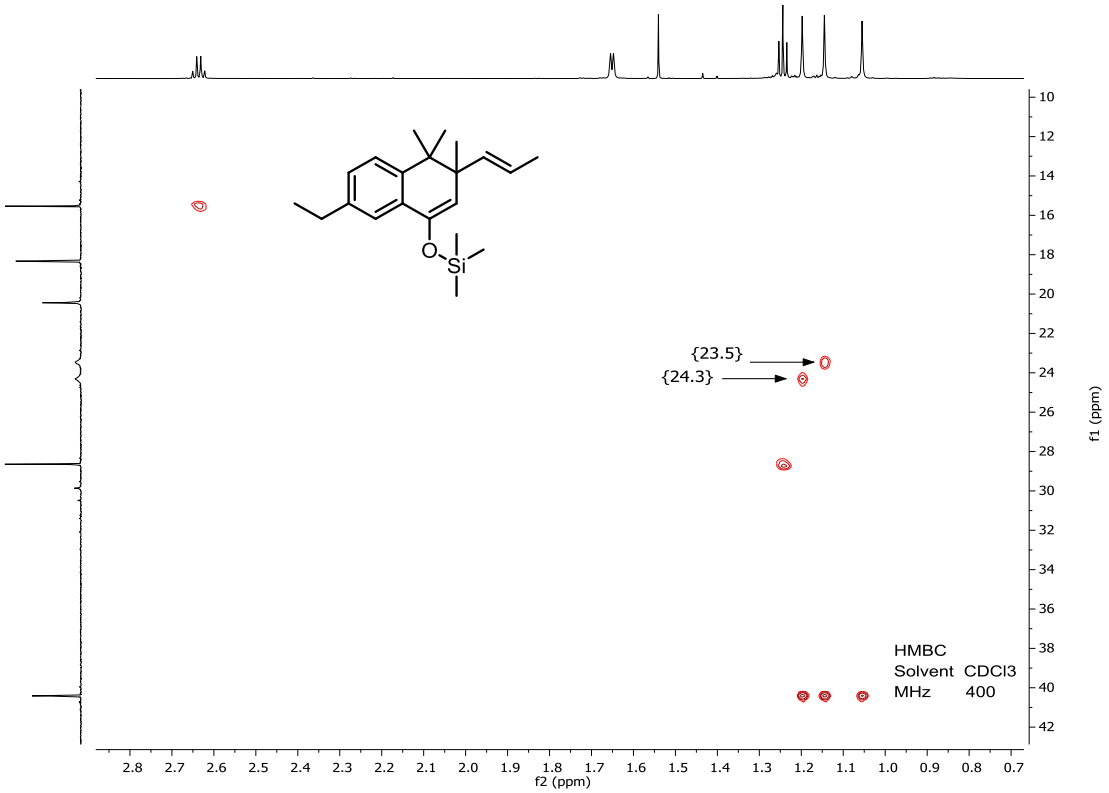

Solvent CDCl3
MHz 400
Nucleus 1H
0.92
0.98
1.00
0.93
0.98
3.00
0.89
1.03
2.85
3.01
3.05
2.92
f1 (ppm)

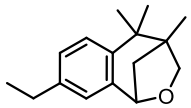

198.2
157.8
144.9
135.8
131.9
127.8
124.5
122.3
108.8
55.6
48.0
43.6
40.4
27.0
24.8
21.7
18.5
Solvent CDCl3
MHz 101
Nucleus 13C
13C signals marked with an asterisk are visible as cross-peaks in the HMBC spectrum
f1 (ppm)

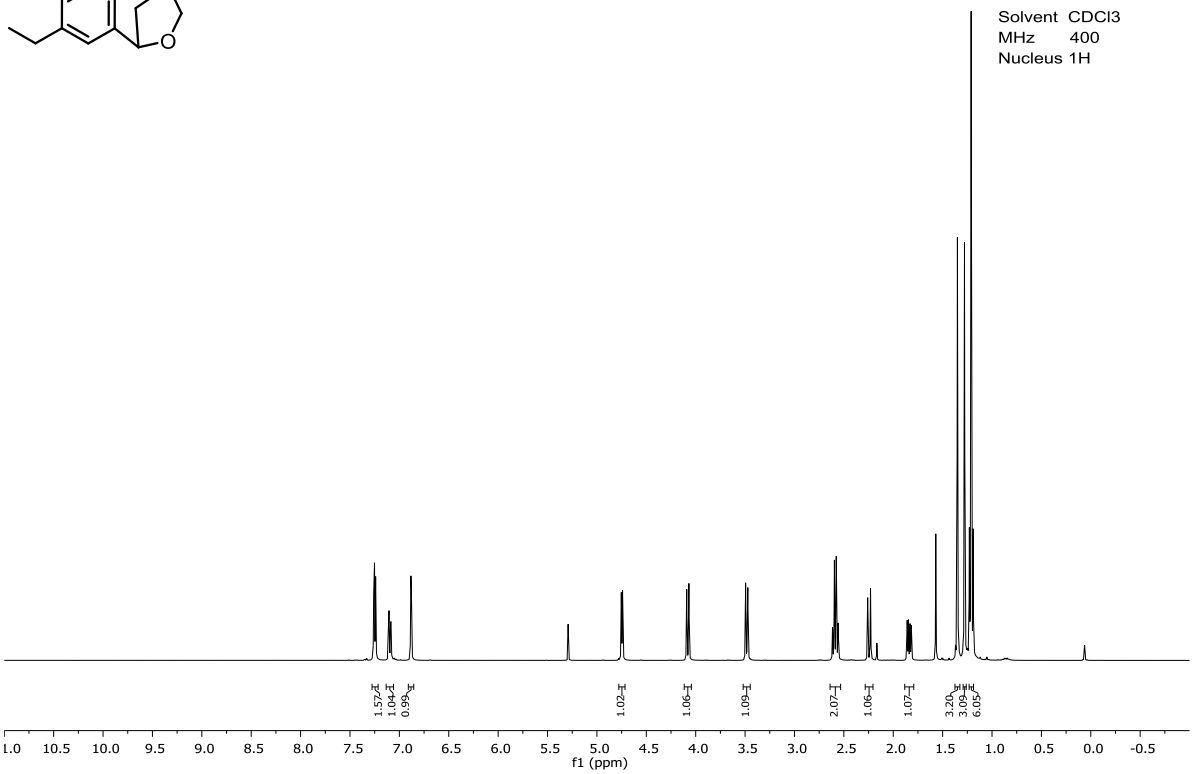

{24.8}
{27.0}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

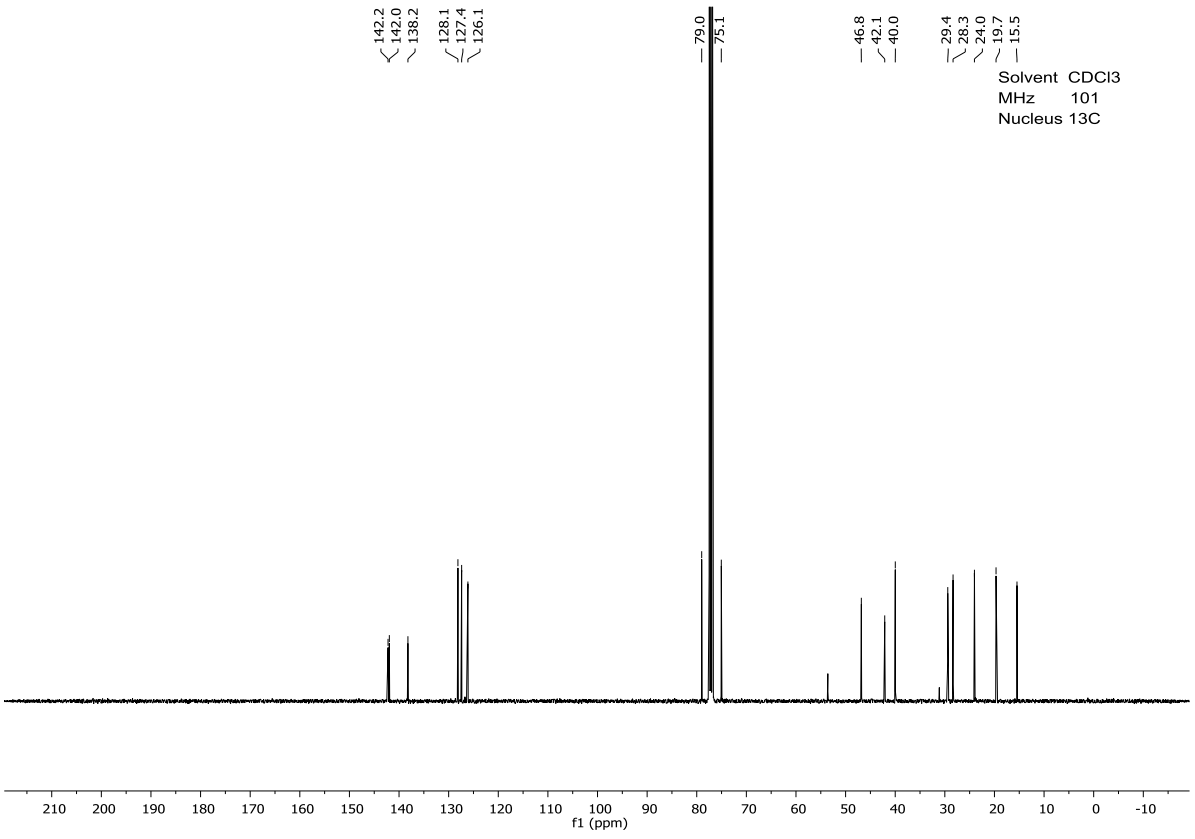

Solvent CDCl3
MHz 800
Nucleus 1H
1.02
1.02
2.09
1.02
2.07
2.94
3.82
2.95
3.00
2.94
9.16
f1 (ppm)

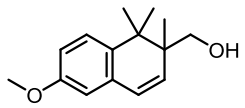

146.1
143.2
141.4
135.9
131.3
127.5
124.3
123.1
121.6
115.6
44.0
40.4
28.6
24.3
23.5
20.4
18.3
15.5
0.5
Solvent CDCl3
MHz 201
Nucleus 13C
13C signals marked with an asterisk are visible as cross-peaks in the HMBC spectrum
f1 (ppm)


{23.5}
{24.3}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

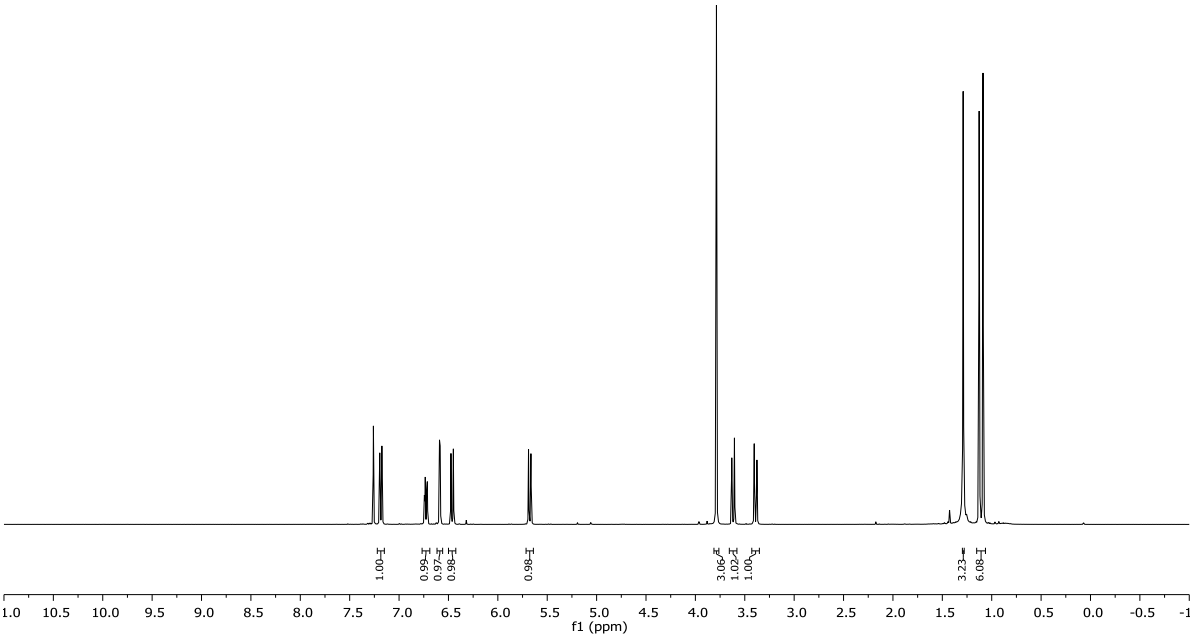


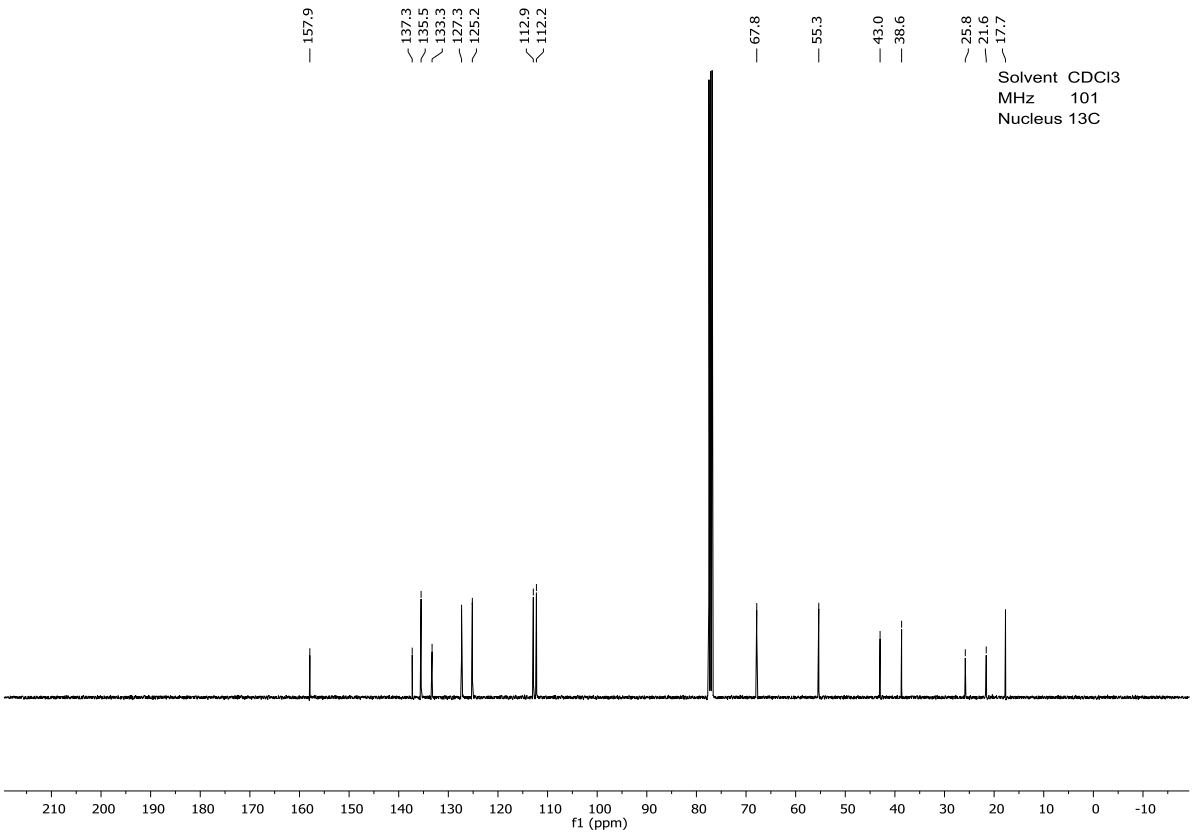

Solvent CDCl3
MHz 400
Nucleus 1H
1.57
1.04
0.99
1.02
1.06
1.09
2.07
1.06
1.07
3.20
3.09
6.05
f1 (ppm)

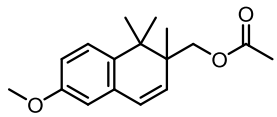

142.2
142.0
138.2
128.1
127.4
126.1
79.0
75.1
46.8
42.1
40.0
29.4
28.3
24.0
19.7
15.5
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

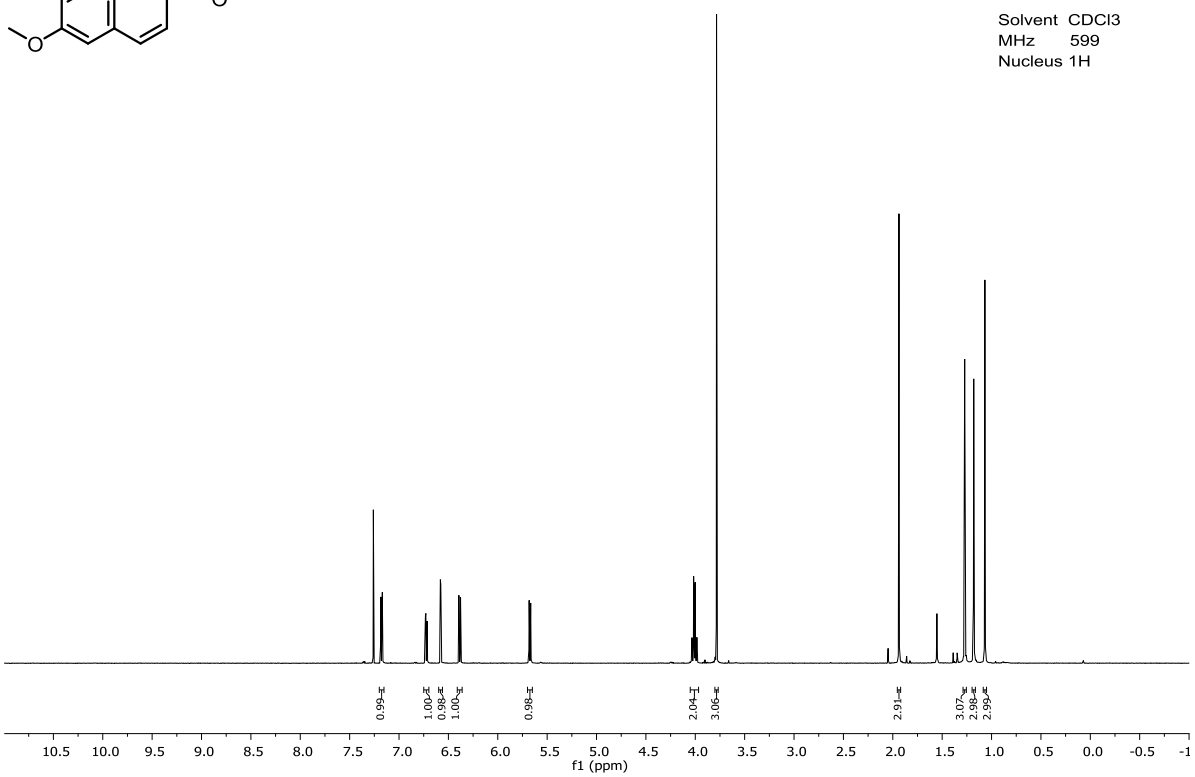


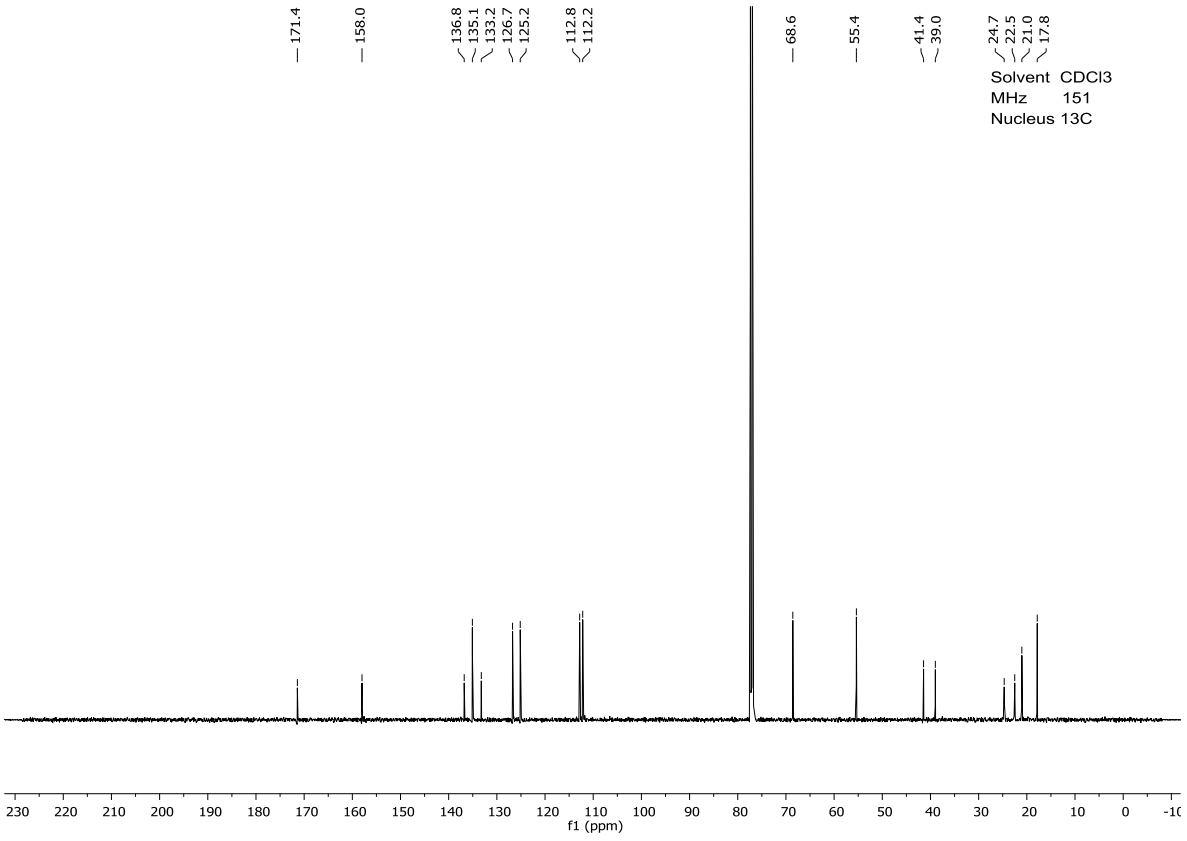
Solvent CDCl3
MHz 400
Nucleus 1H

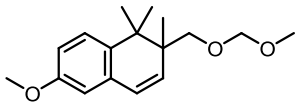




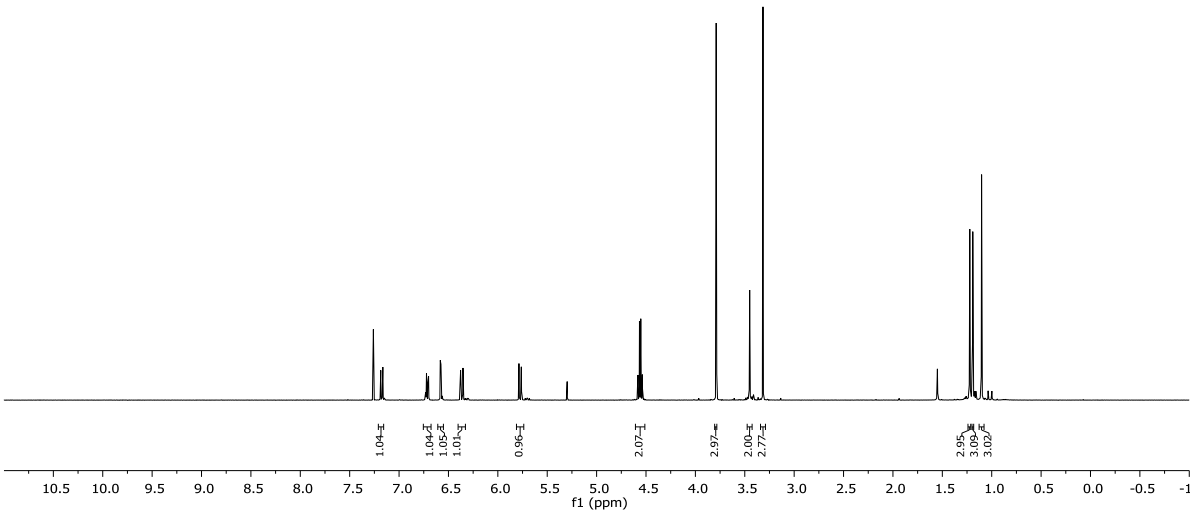



Solvent CDCl3
MHz 599
Nucleus 1H
0.99
1.00
0.98
1.00
0.98
2.04
3.06
2.91
3.07
2.98
2.99
f1 (ppm)


171.4
158.0
136.8
135.1
133.2
126.7
125.2
112.8
112.2
68.6
55.4
41.4
39.0
24.7
22.5
21.0
17.8
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

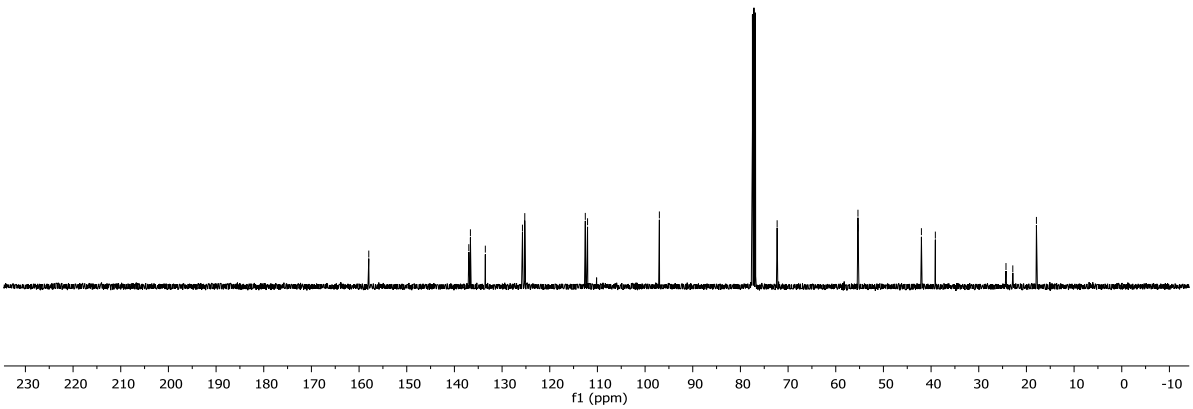


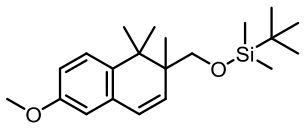
Solvent CDCl3
MHz 400
Nucleus 1H



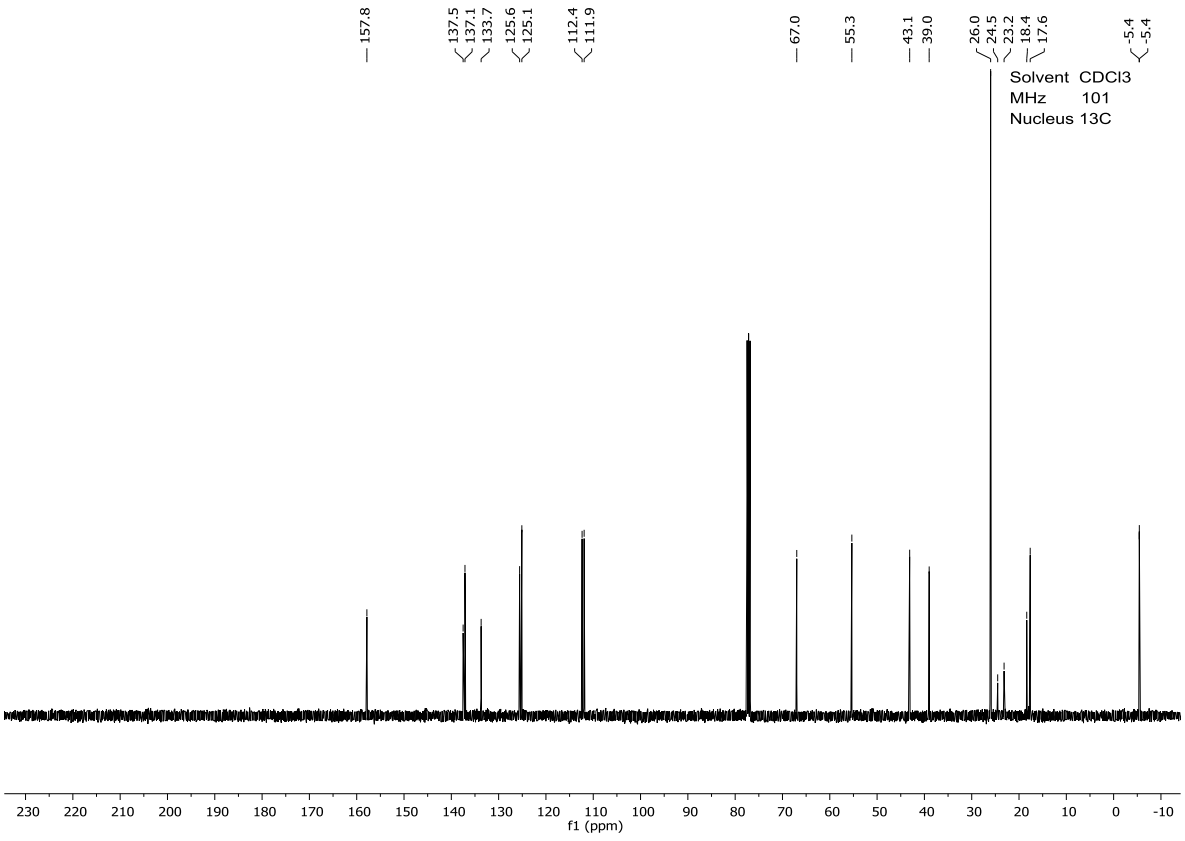
158.0
137.0
136.6
133.5
125.7
125.2
112.5
112.1
97.0
72.3
55.3
55.3
42.0
39.1
24.3
22.9
17.9

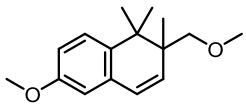
Solvent CDCl3
MHz 101
Nucleus 13C

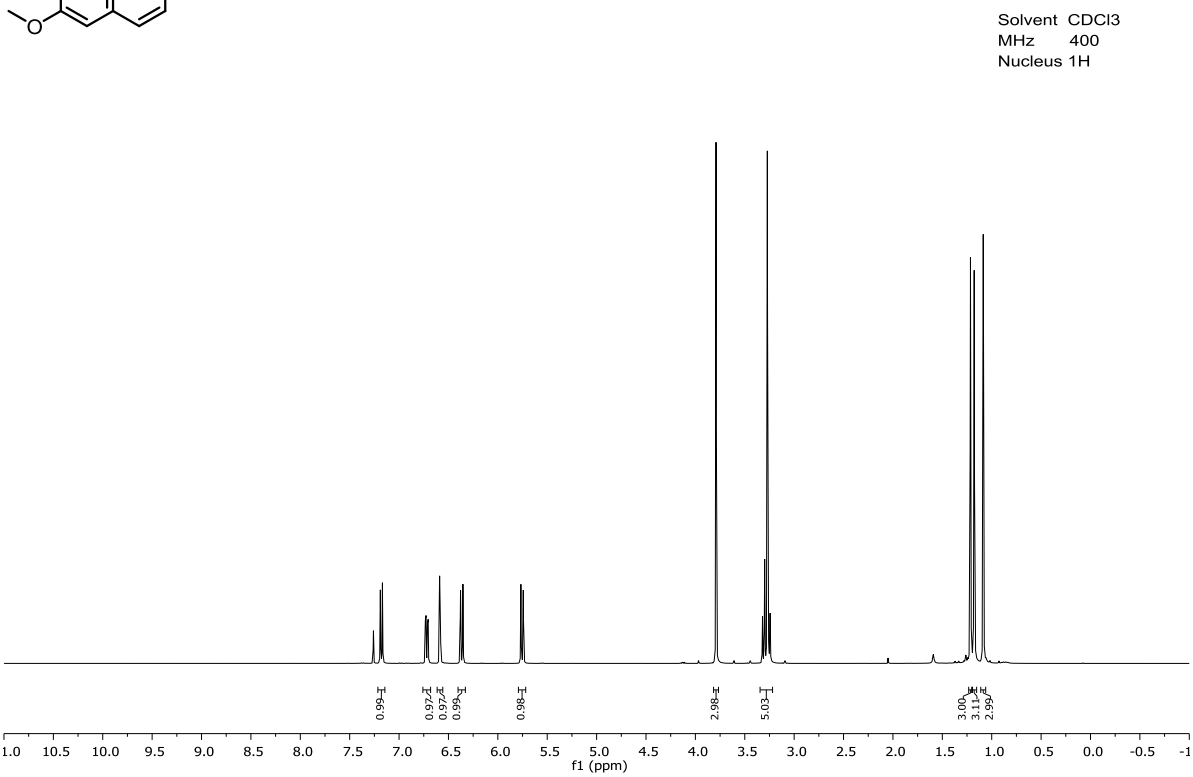


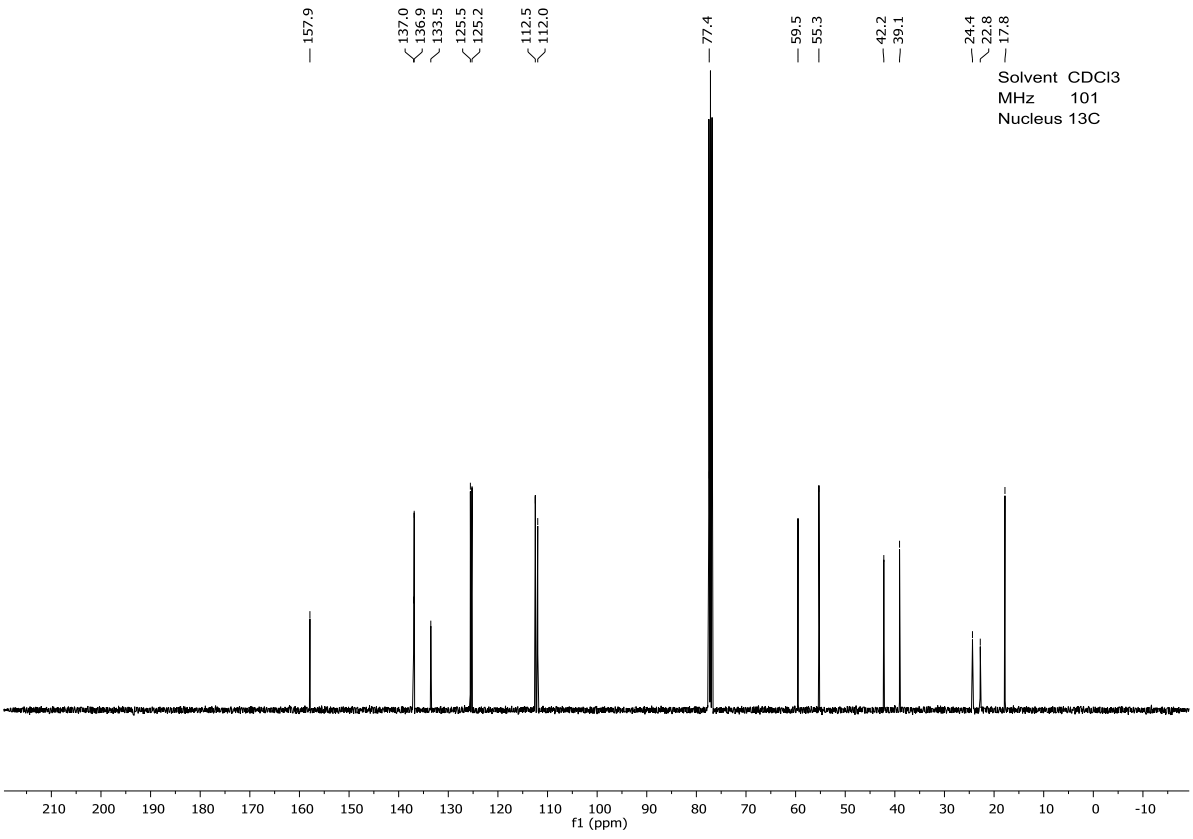


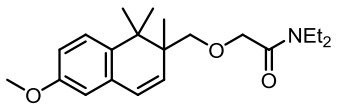
Solvent CDCl3
MHz 400
Nucleus 1H
1.00
0.95
0.95
0.99
0.97
3.05
2.01
5.96
3.08
9.03
5.74
f1 (ppm)


157.8
137.5
137.1
133.7
125.6
125.1
112.4
111.9
67.0
55.3
43.1
39.0
26.0
24.5
23.2
18.4
17.6
-5.4
-5.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

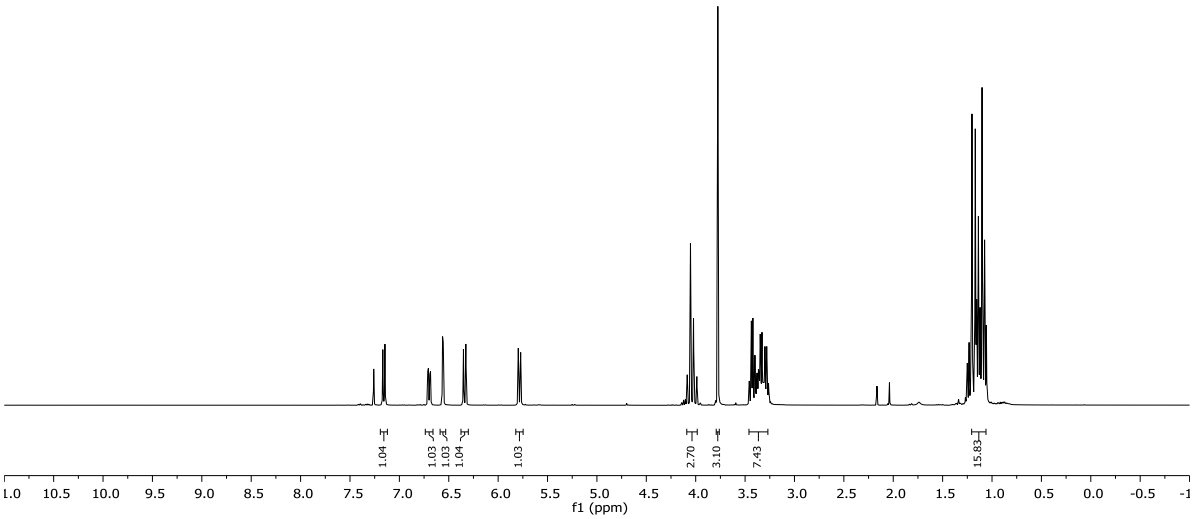


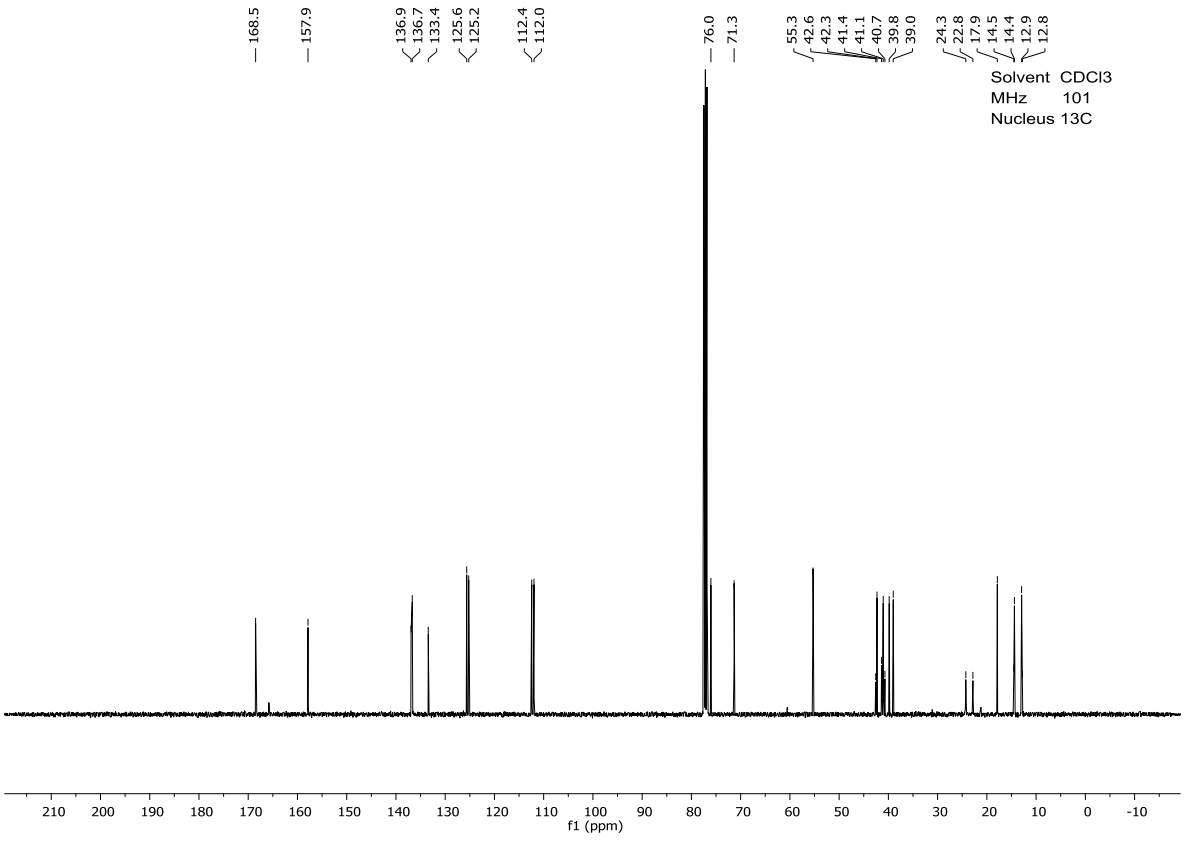

Solvent CDCl3
MHz 400
Nucleus 1H
0.99
0.97
0.97
0.99
0.98
2.98
5.03
3.00
3.11
2.99
f1 (ppm)


157.9
137.0
136.9
133.5
125.5
125.2
112.5
112.0
77.4
59.5
55.3
42.2
39.1
24.4
22.8
17.8
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

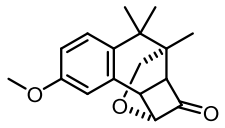


Solvent CDCl3
MHz 400
Nucleus 1H

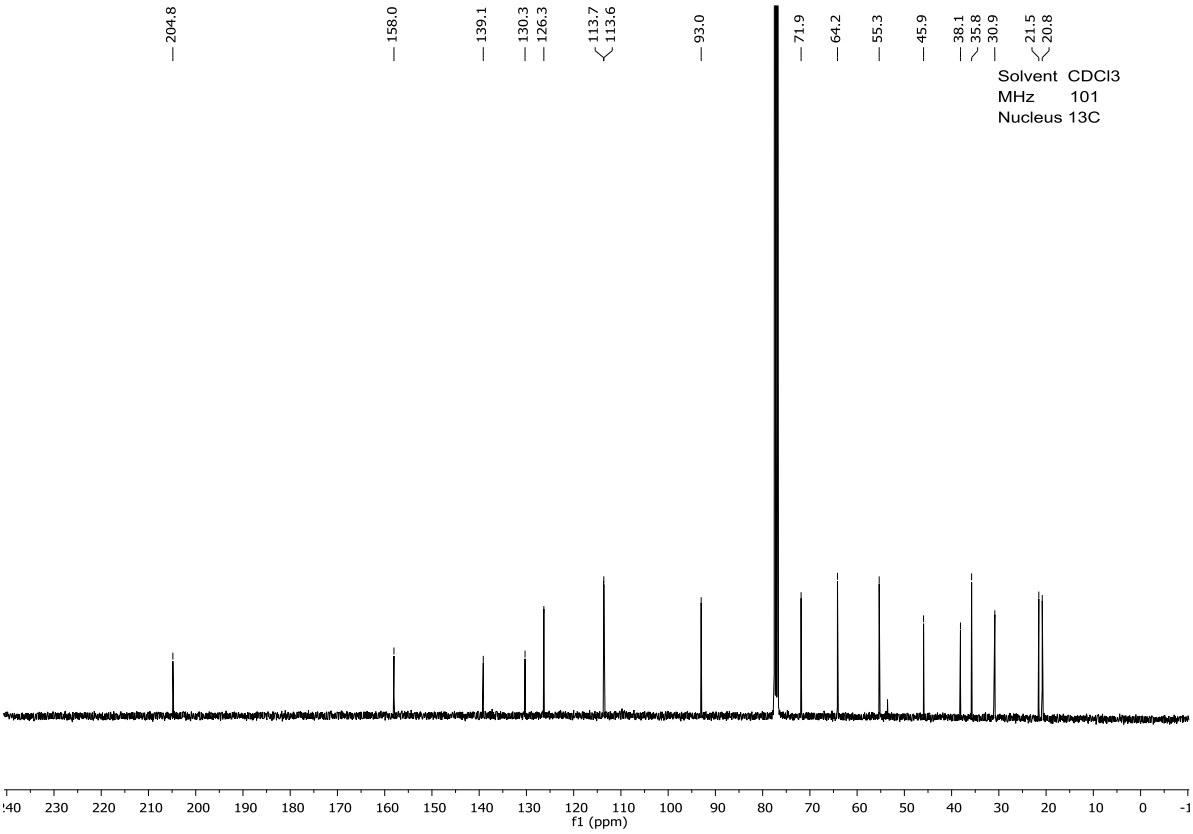


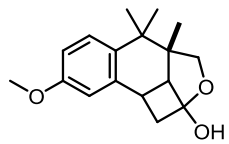


Solvent CDCl3
MHz 101
Nucleus 13C

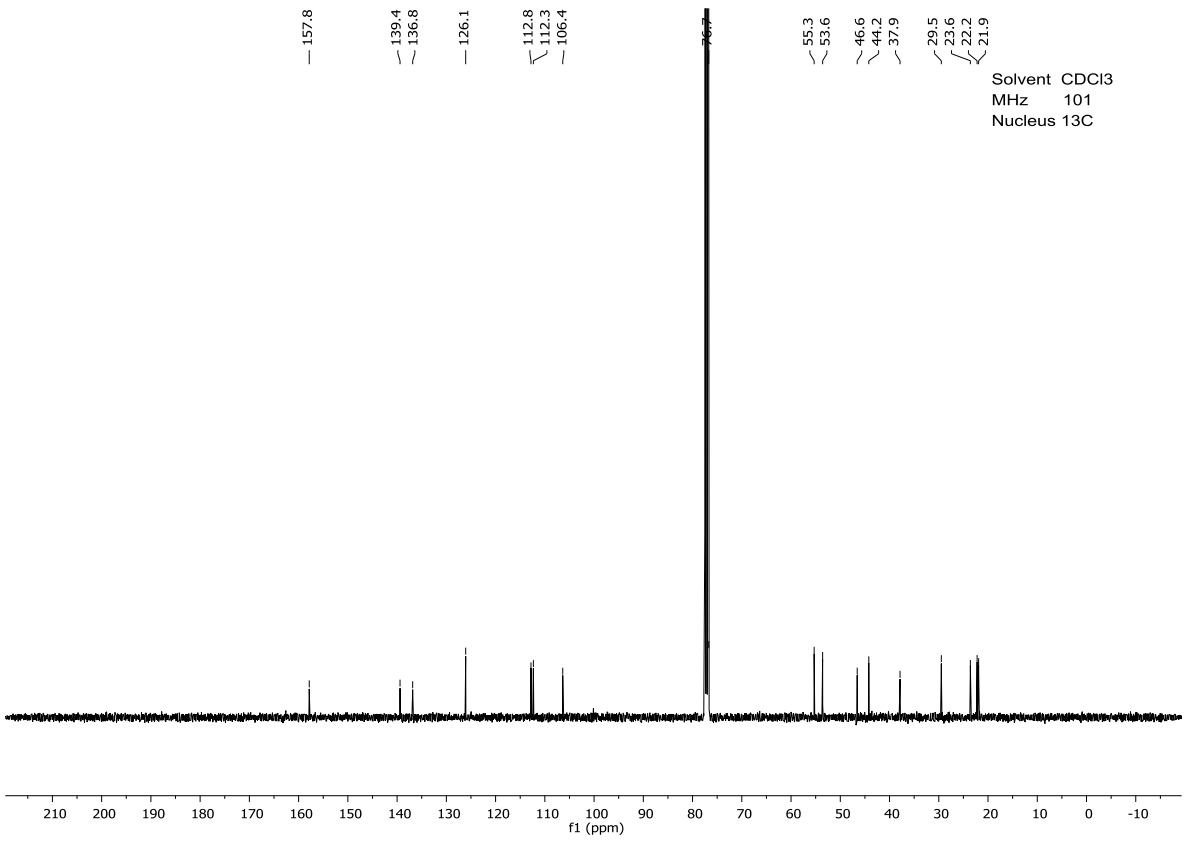


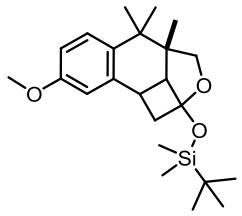
Solvent CDCl3
MHz 400
Nucleus 1H
0.98
0.99
0.93
1.00
1.01
2.99
0.98
0.99
1.02
2.90
3.05
3.04
f1 (ppm)


204.8
158.0
139.1
130.3
126.3
113.7
113.6
93.0
71.9
64.2
55.3
45.9
38.1
35.8
30.9
21.5
20.8
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

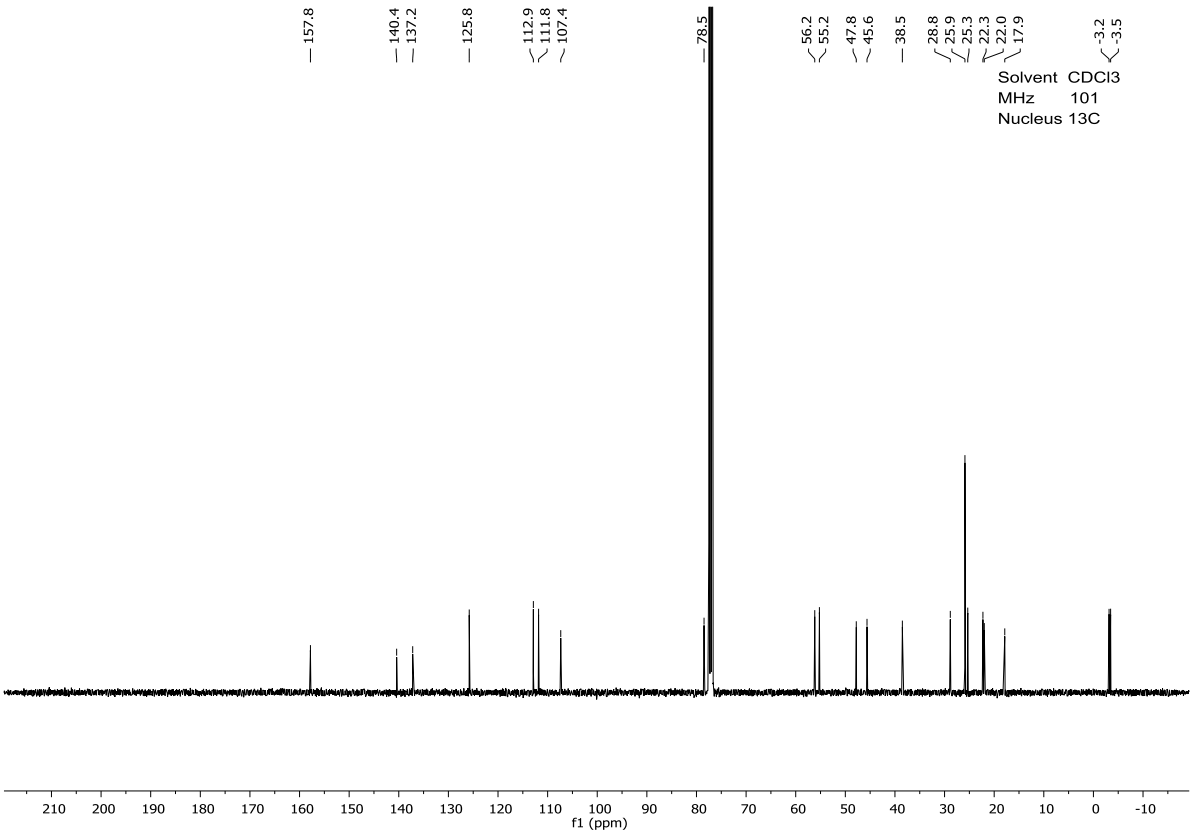

O
O
OH

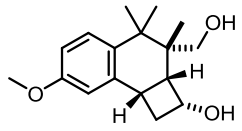
Solvent CDCl3
MHz 400
Nucleus 1H
1.09
1.00
0.97
2.92
1.06
1.04
1.07
1.07
1.87
1.06
6.01
2.94
f1 (ppm)

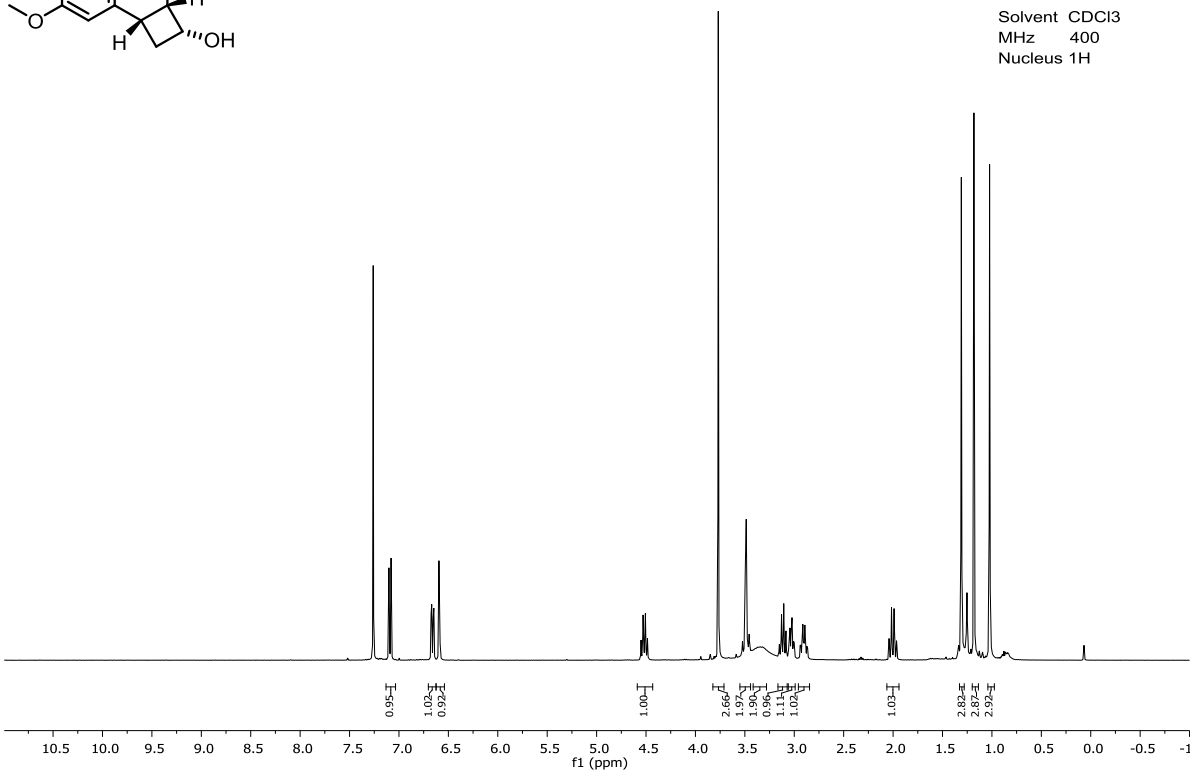

157.8
139.4
136.8
126.1
112.8
112.3
106.4
76.7
55.3
53.6
46.6
44.2
37.9
29.5
23.6
22.2
21.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

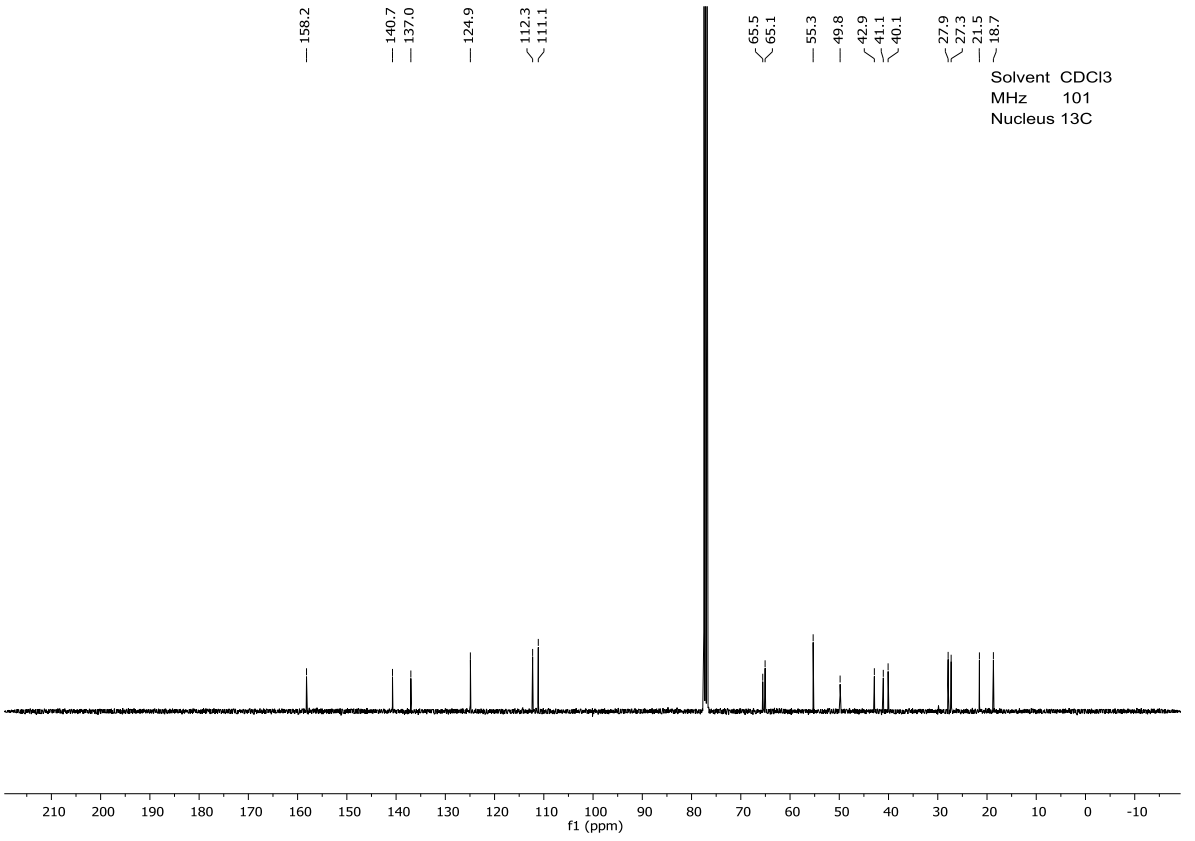

O
O
O
Si

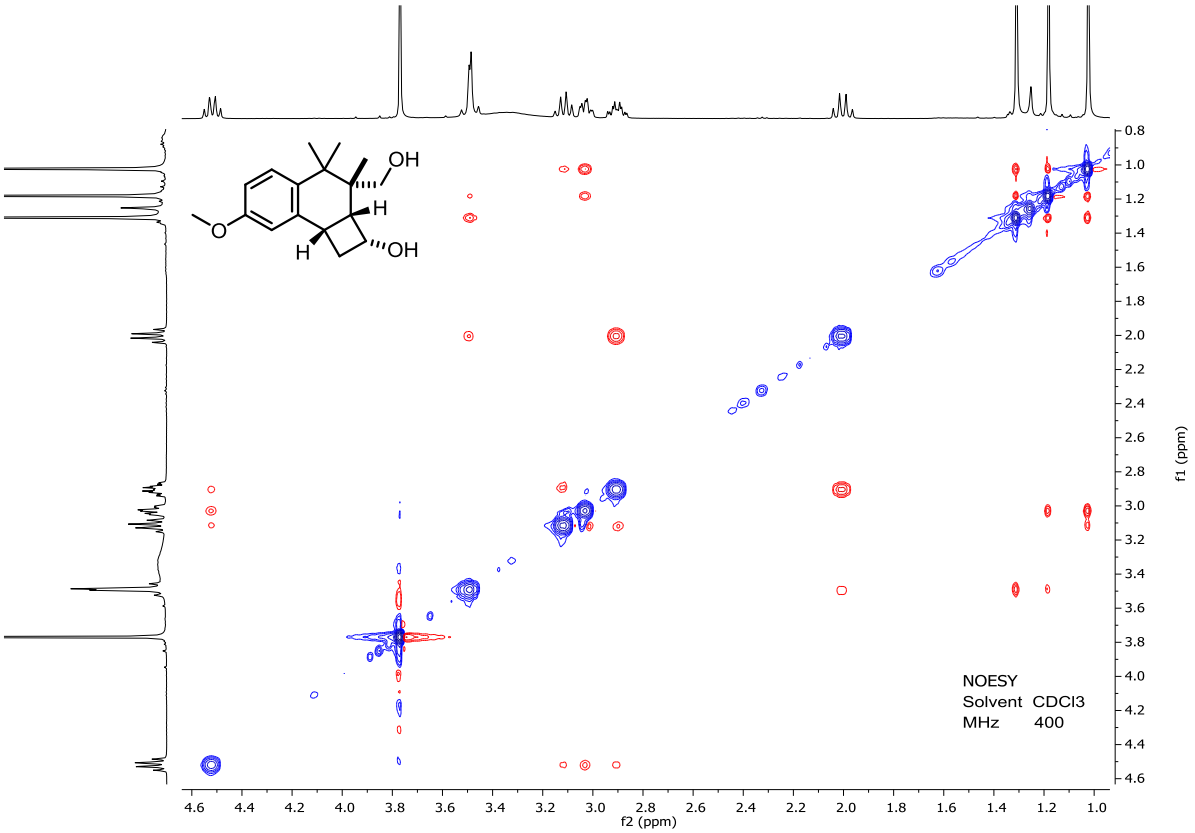
Solvent CDCl3
MHz 400
Nucleus 1H
0.97
0.99
0.98
2.96
1.03
1.02
1.02
1.01
1.00
1.03
6.01
2.98
9.16
5.83
f1 (ppm)

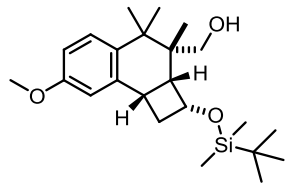

157.8
140.4
137.2
125.8
112.9
111.8
107.4
78.5
56.2
55.2
47.8
45.6
38.5
28.8
25.9
25.3
22.3
22.0
17.9
-3.2
-3.5
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


OH
H
O
H
OH

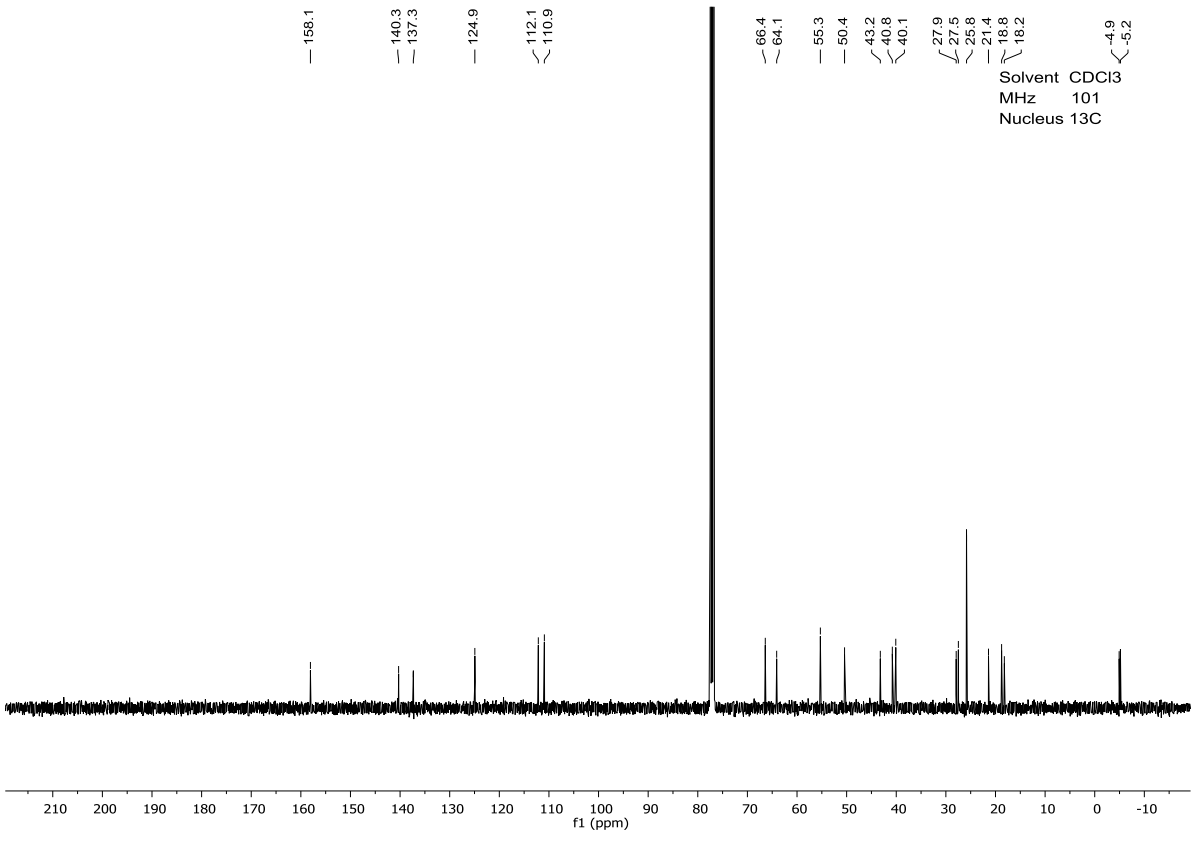

Solvent CDCl3
MHz 400
Nucleus 1H
0.95
1.02
0.92
1.00
2.66
1.97
1.90
0.96
1.11
1.02
1.03
2.82
2.87
2.92
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

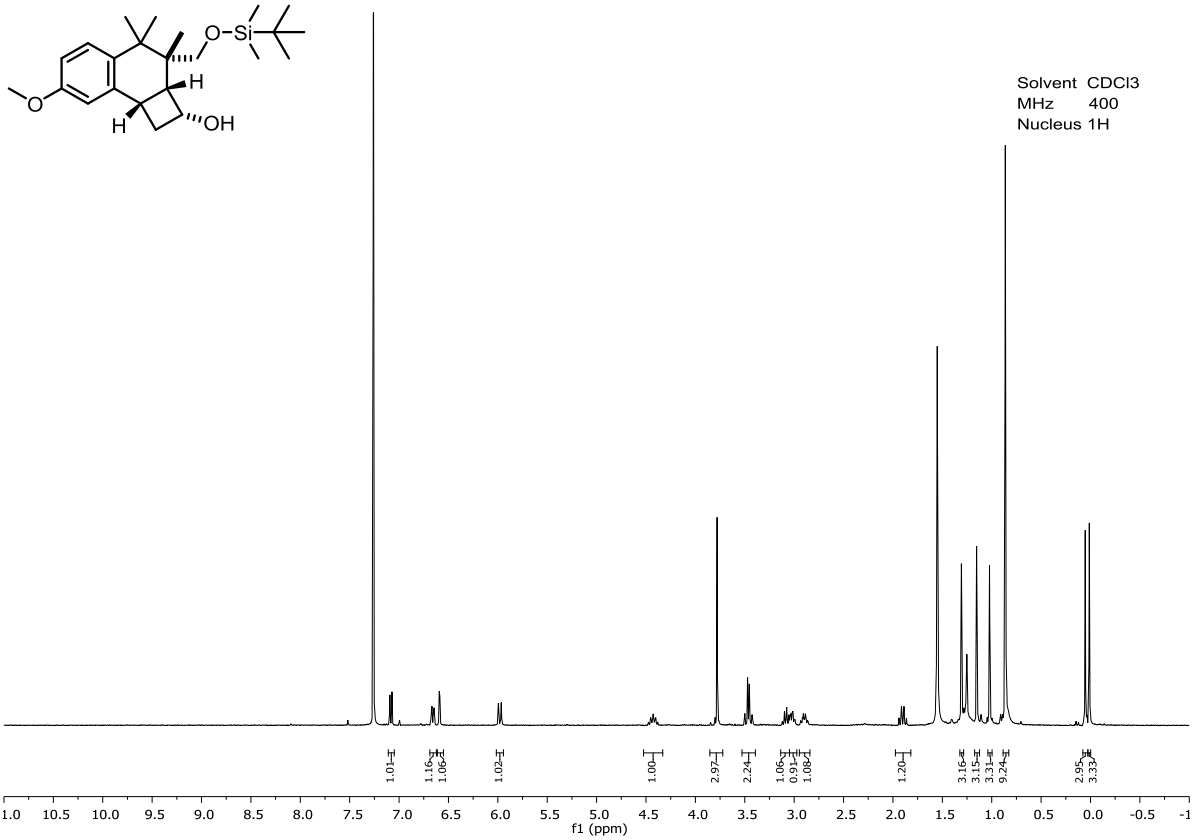

158.2
140.7
137.0
124.9
112.3
111.1
65.5
65.1
55.3
49.8
42.9
41.1
40.1
27.9
27.3
21.5
18.7
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

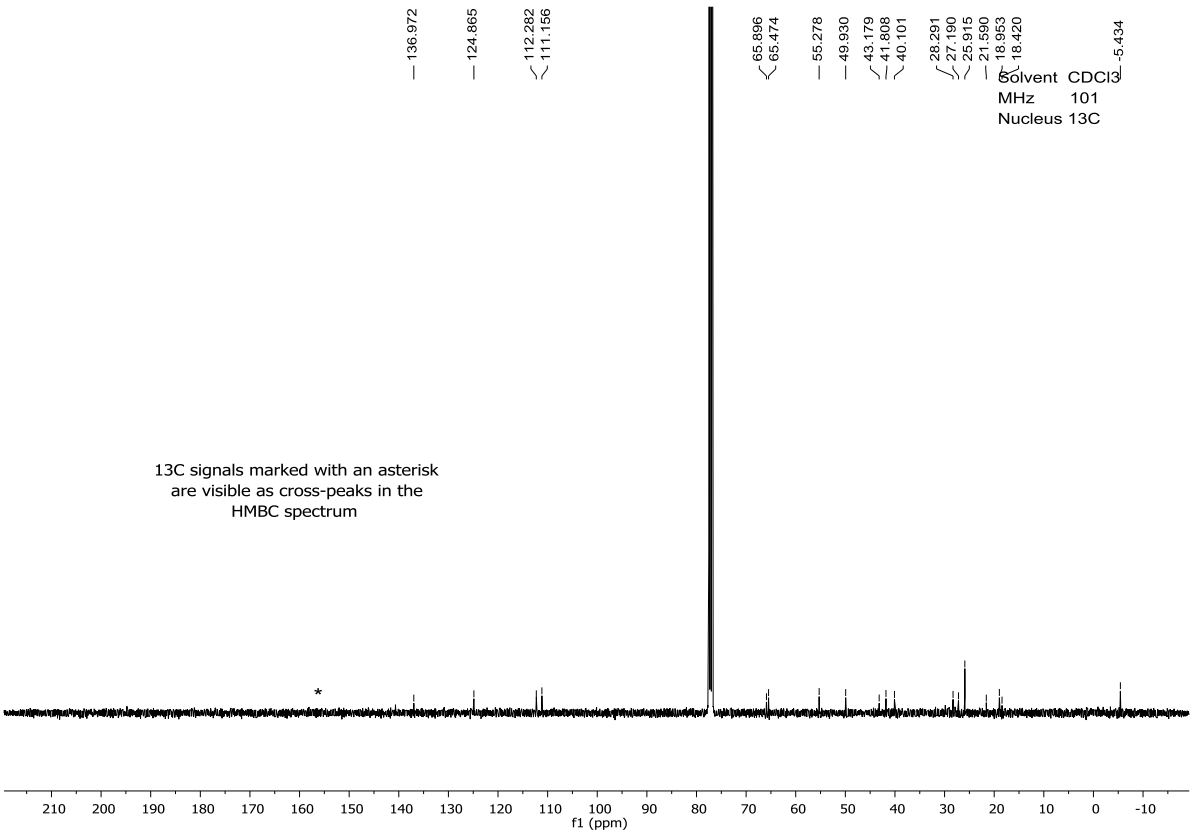

OH
H
O
H
OH
NOESY
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

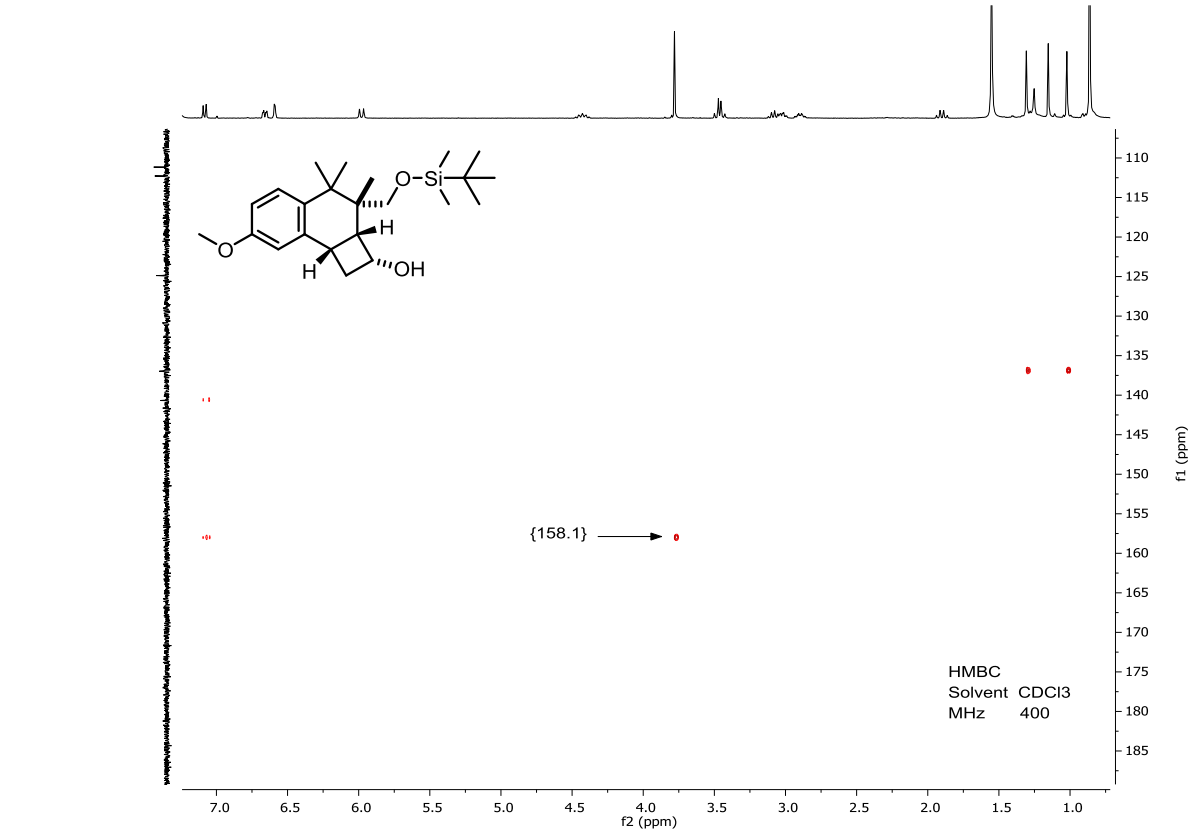

OH
H
O
H
O
Si

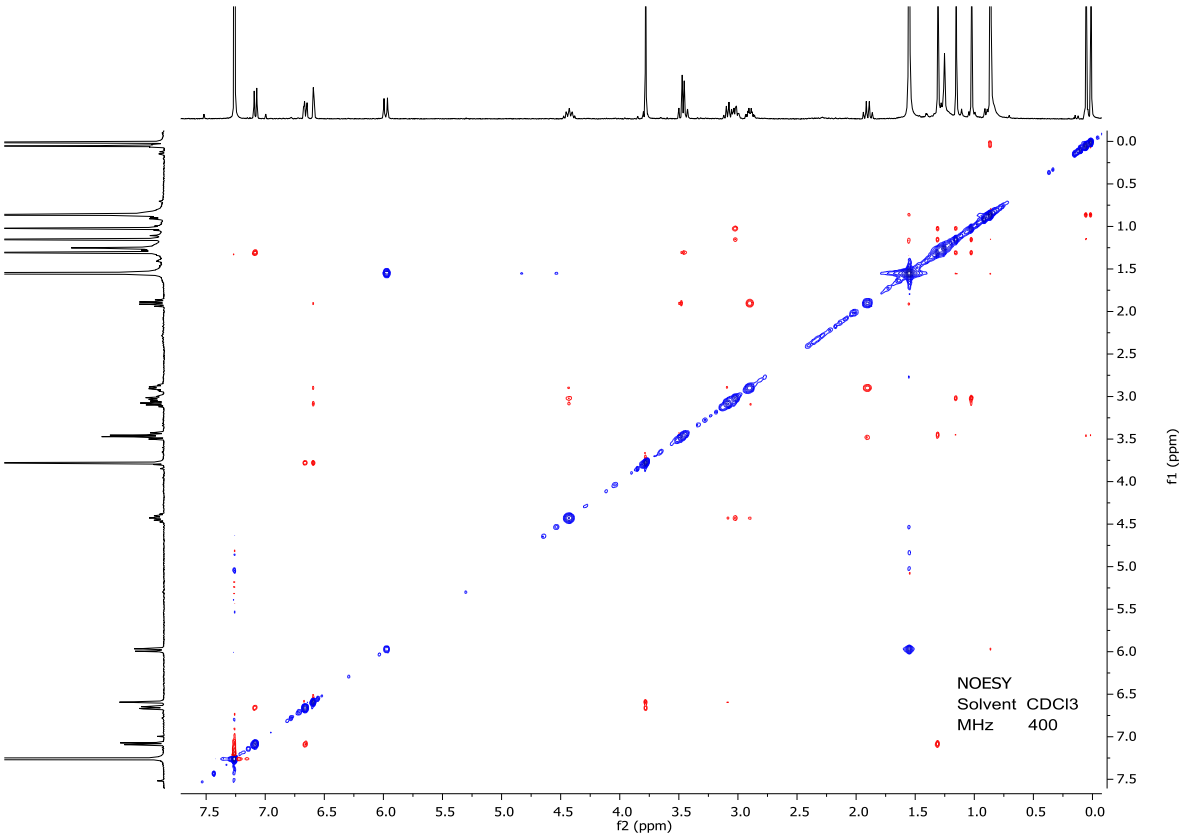
Solvent CDCl3
MHz 400
Nucleus 1H
1.02
1.02
0.99
0.96
1.05
2.95
1.02
2.11
1.08
1.09
1.07
3.07
2.99
2.96
9.05
5.89
f1 (ppm)

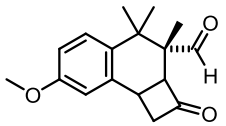

158.1
140.3
137.3
124.9
112.1
110.9
66.4
64.1
55.3
50.4
43.2
40.8
40.1
27.9
27.5
25.8
21.4
18.8
18.2
-4.9
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


Solvent CDCl3
MHz 400
Nucleus 1H
f1 (ppm)

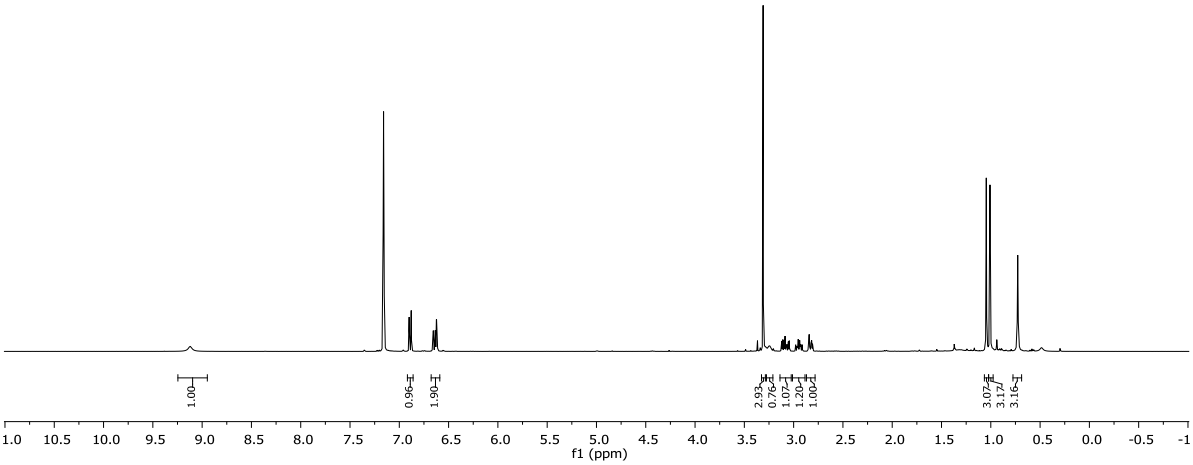

136.972
124.865
112.282
111.156
65.896
65.474
55.278
49.930
43.179
41.808
40.101
28.291
27.190
25.915
21.590
18.953
18.420
-5.434
Solvent CDCl3
MHz 101
Nucleus 13C
13C signals marked with an asterisk
are visible as cross-peaks in the
HMBC spectrum
*
f1 (ppm)

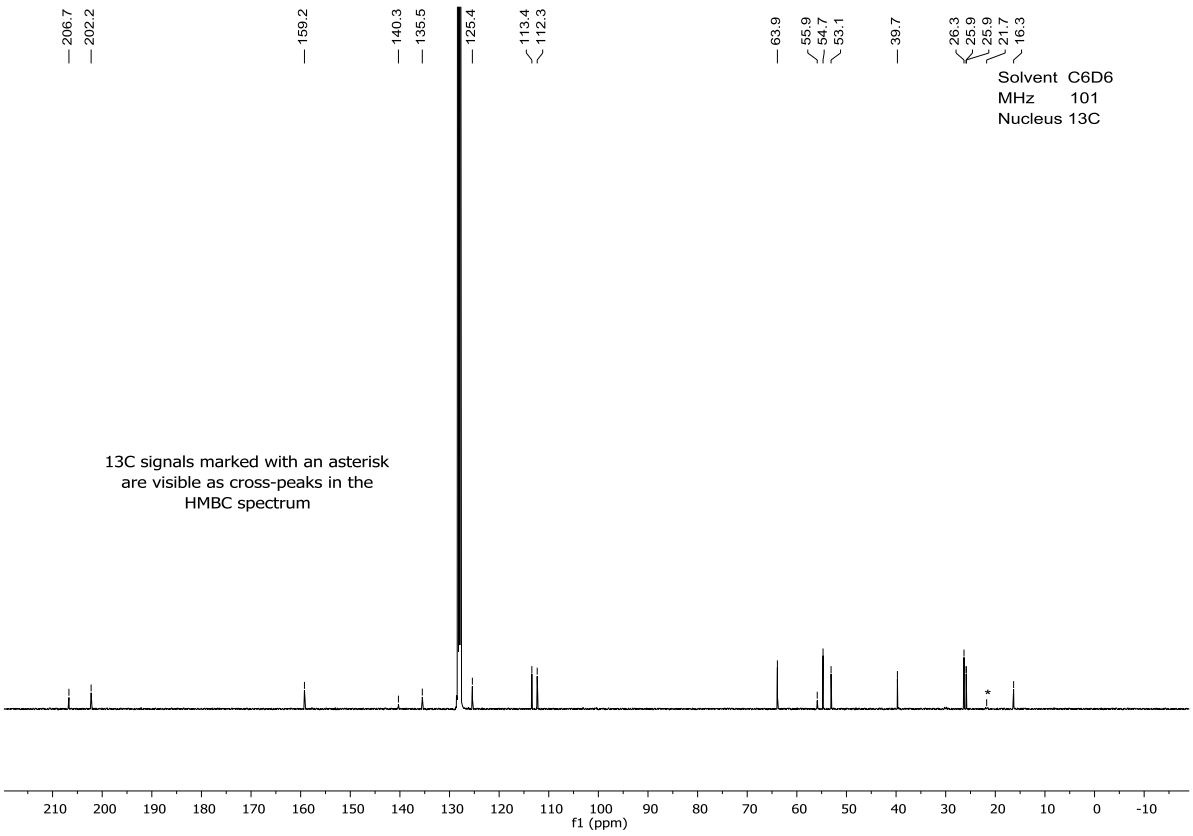

O-Si
H
O
H
OH
{158.1}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)


NOESY
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)



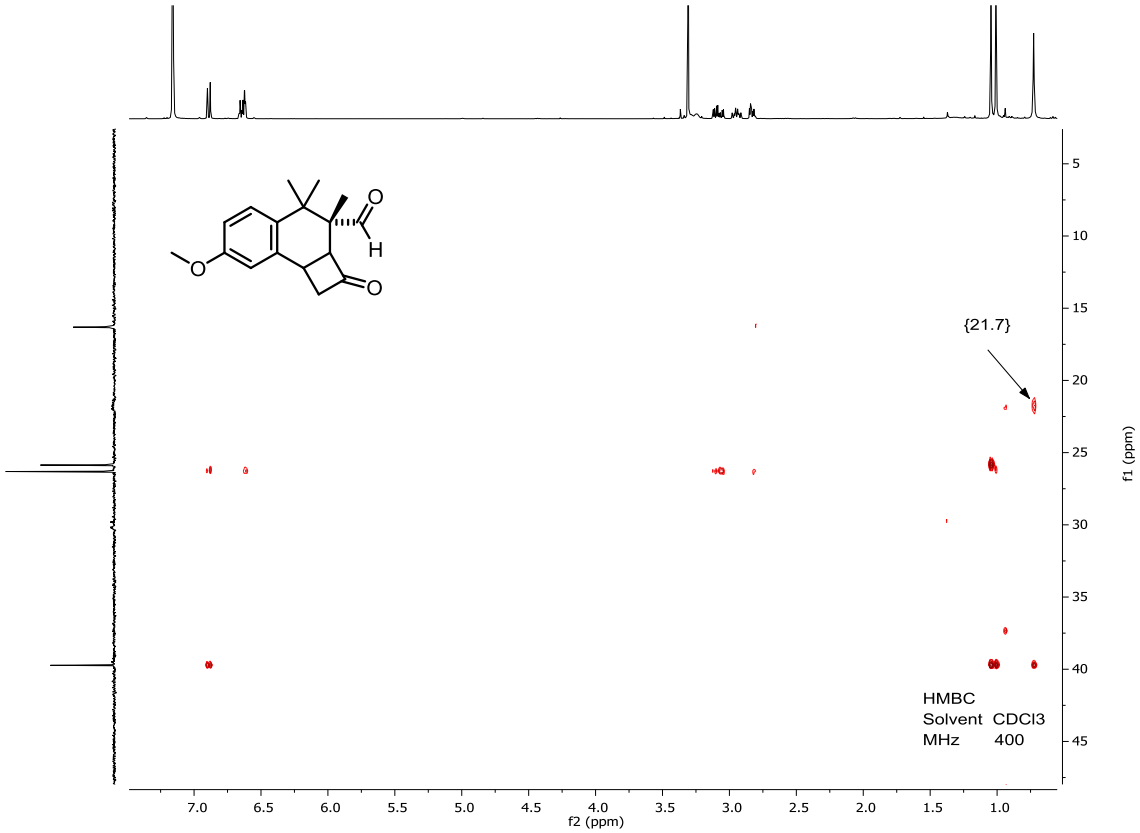
Solvent C6D6
MHz 400
Nucleus 1H

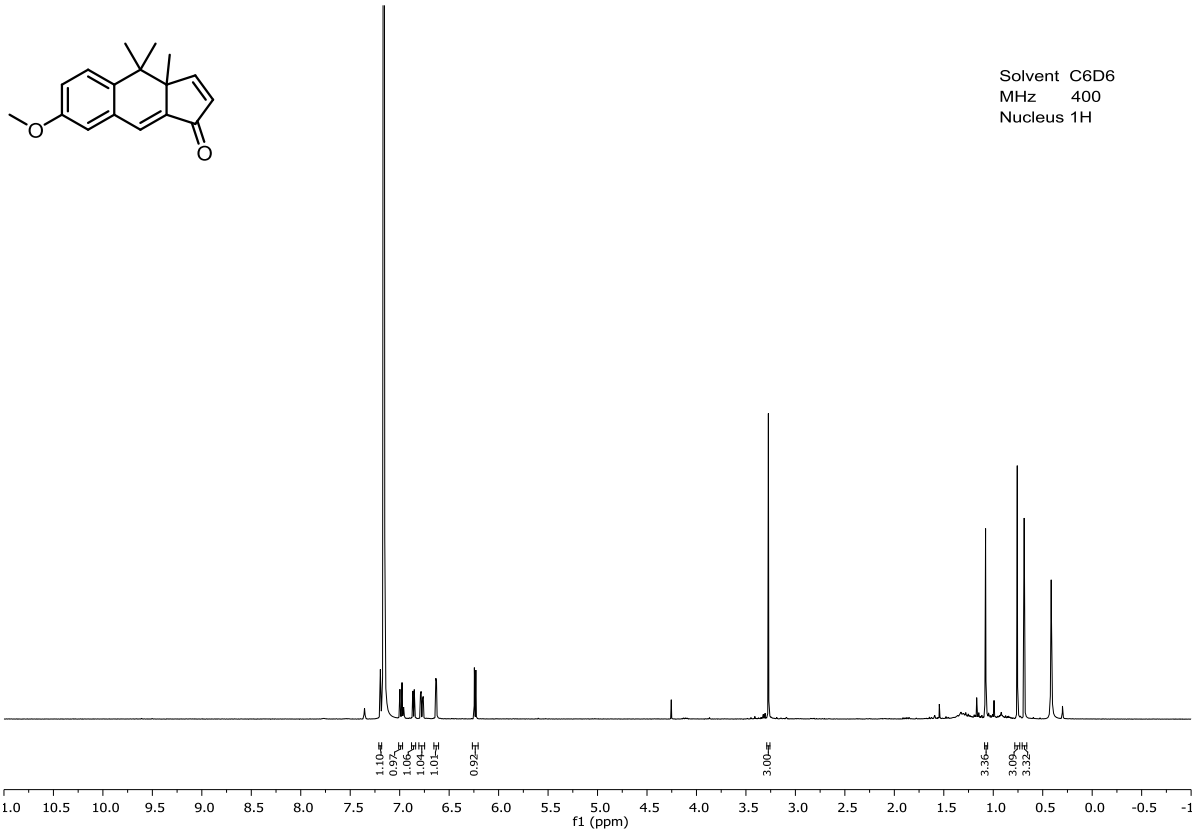


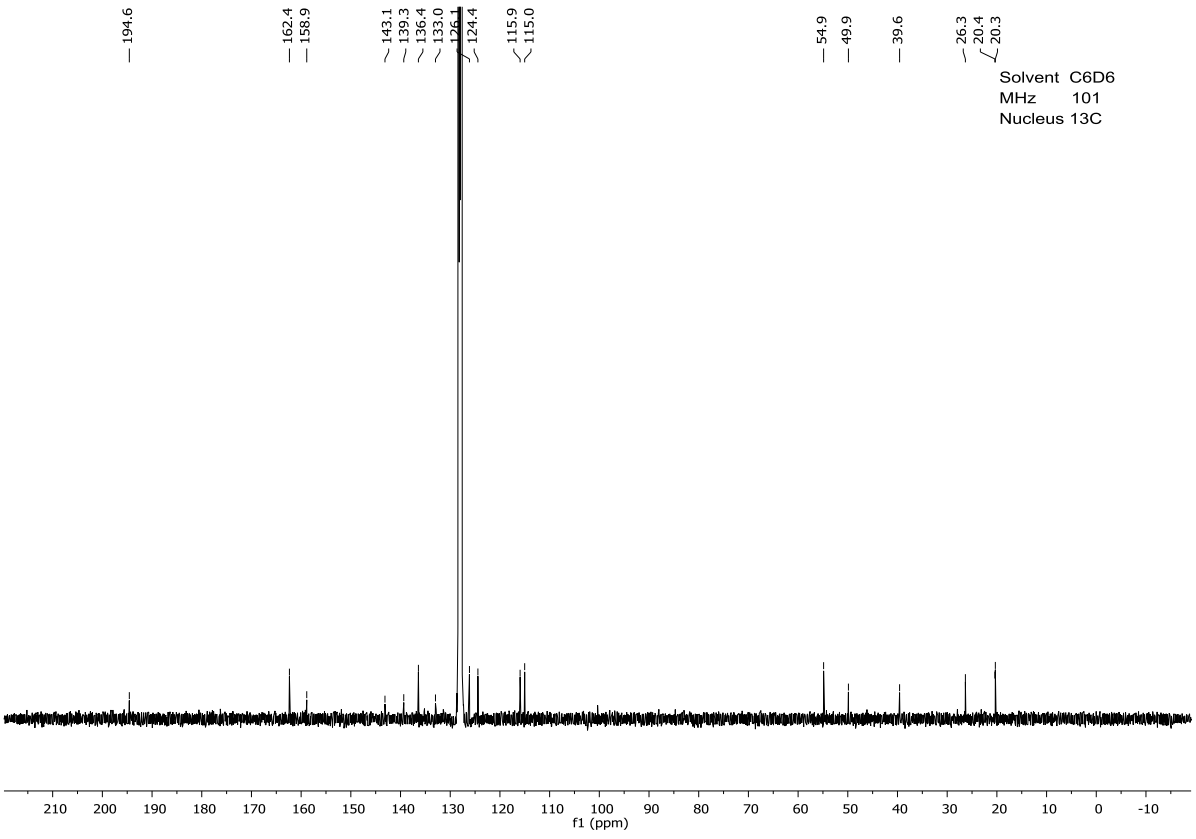


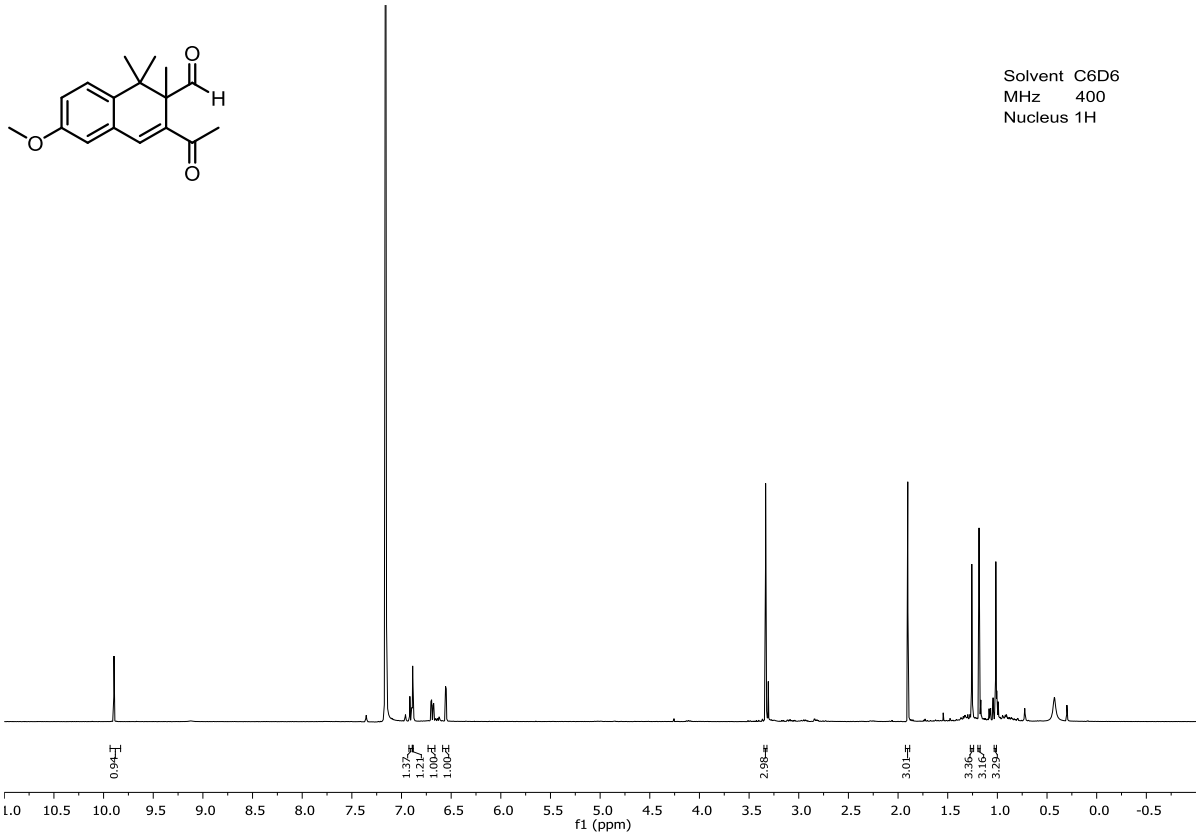
Solvent C6D6
MHz 101
Nucleus 13C

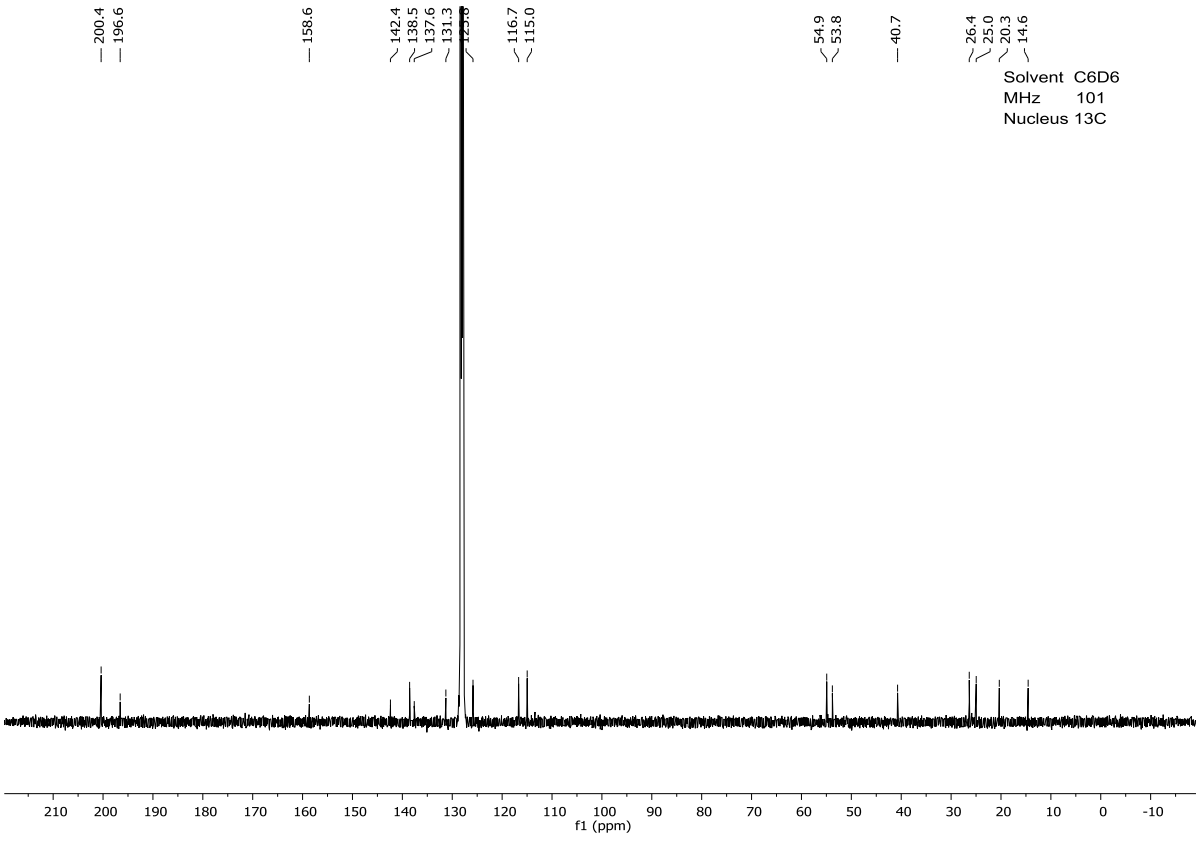
13C signals marked with an asterisk are visible as cross-peaks in the HMBC spectrum

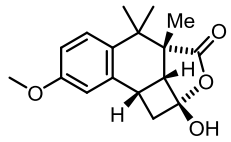

{21.7}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)


Solvent C6D6
MHz 400
Nucleus 1H
1.10
0.92
1.06
1.04
1.01
0.92
3.00
3.36
3.09
3.32
f1 (ppm)

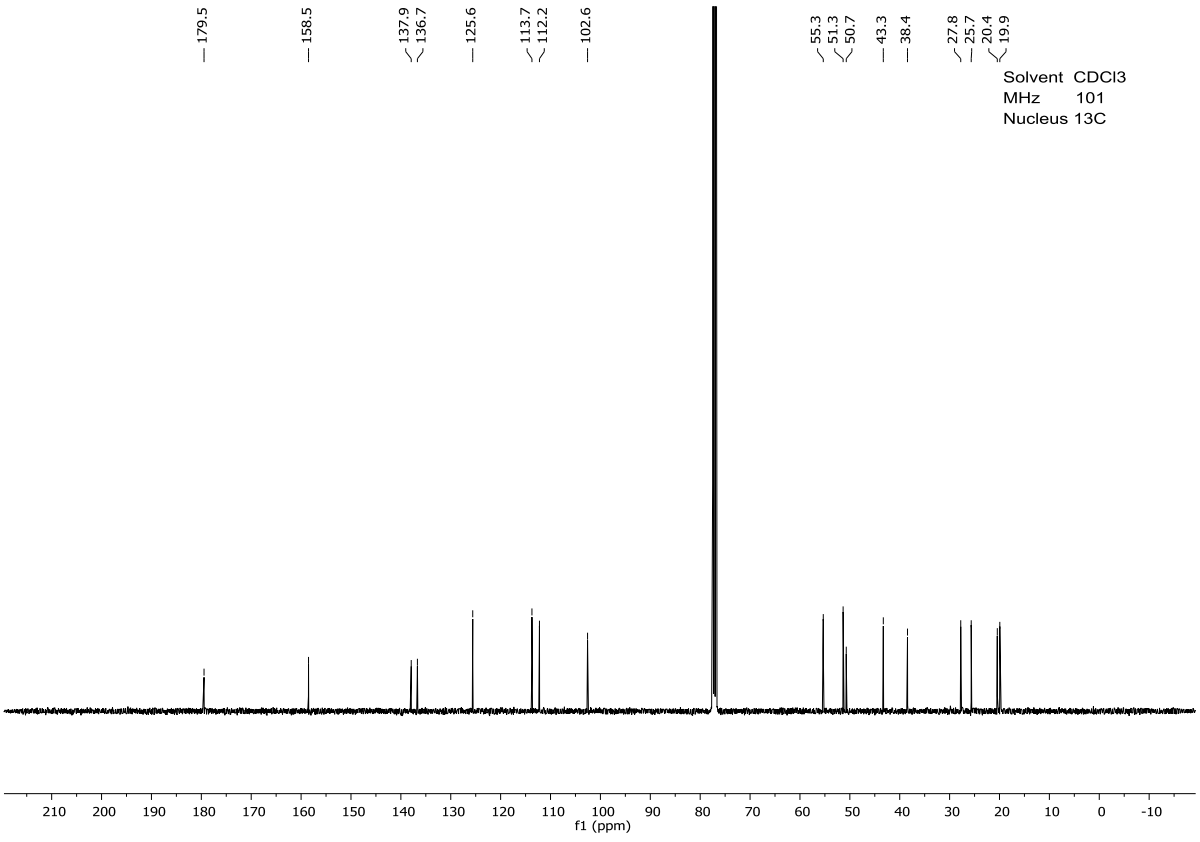

194.6
162.4
158.9
143.1
139.3
136.4
133.0
126.1
124.4
115.9
115.0
54.9
49.9
39.6
26.3
20.4
20.3
Solvent C6D6
MHz 101
Nucleus 13C
f1 (ppm)

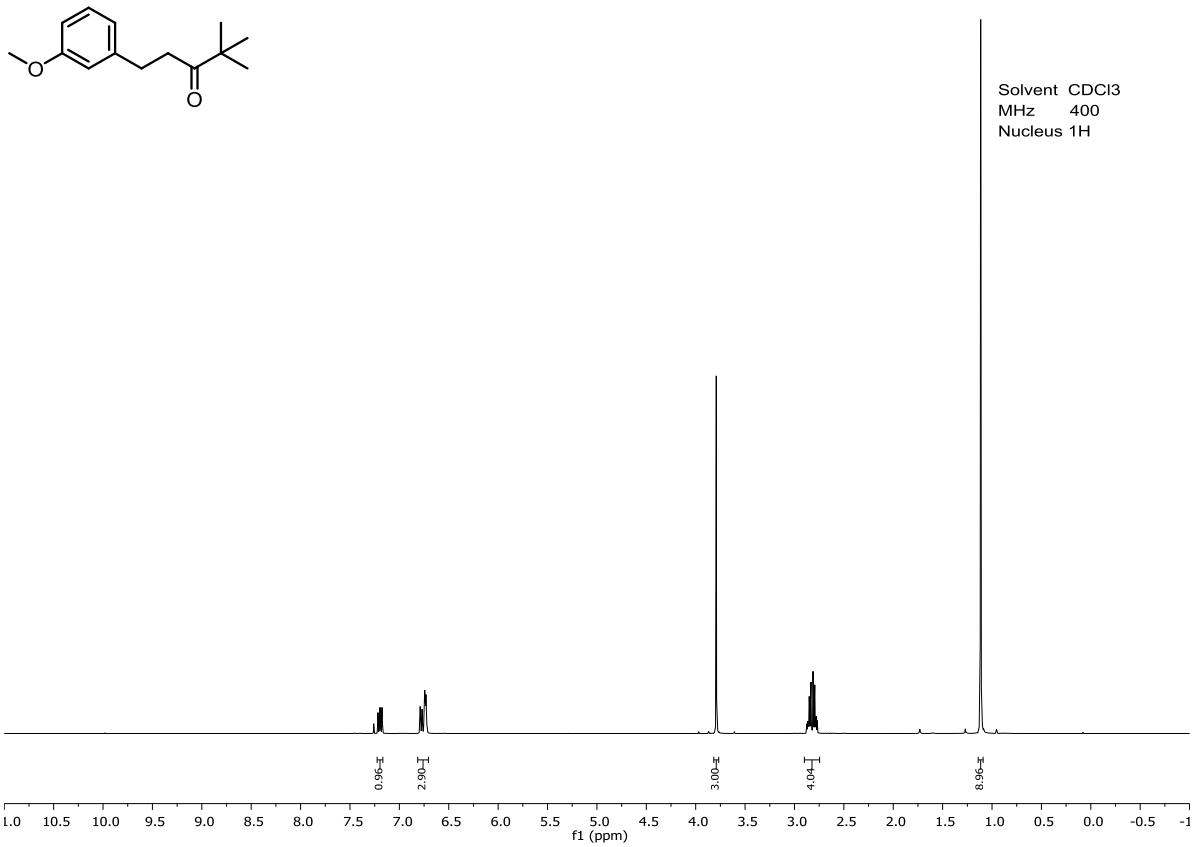

Solvent C6D6
MHz 400
Nucleus 1H
0.94
1.37
1.21
1.00
1.00
2.98
3.01
3.36
3.16
3.29
f1 (ppm)

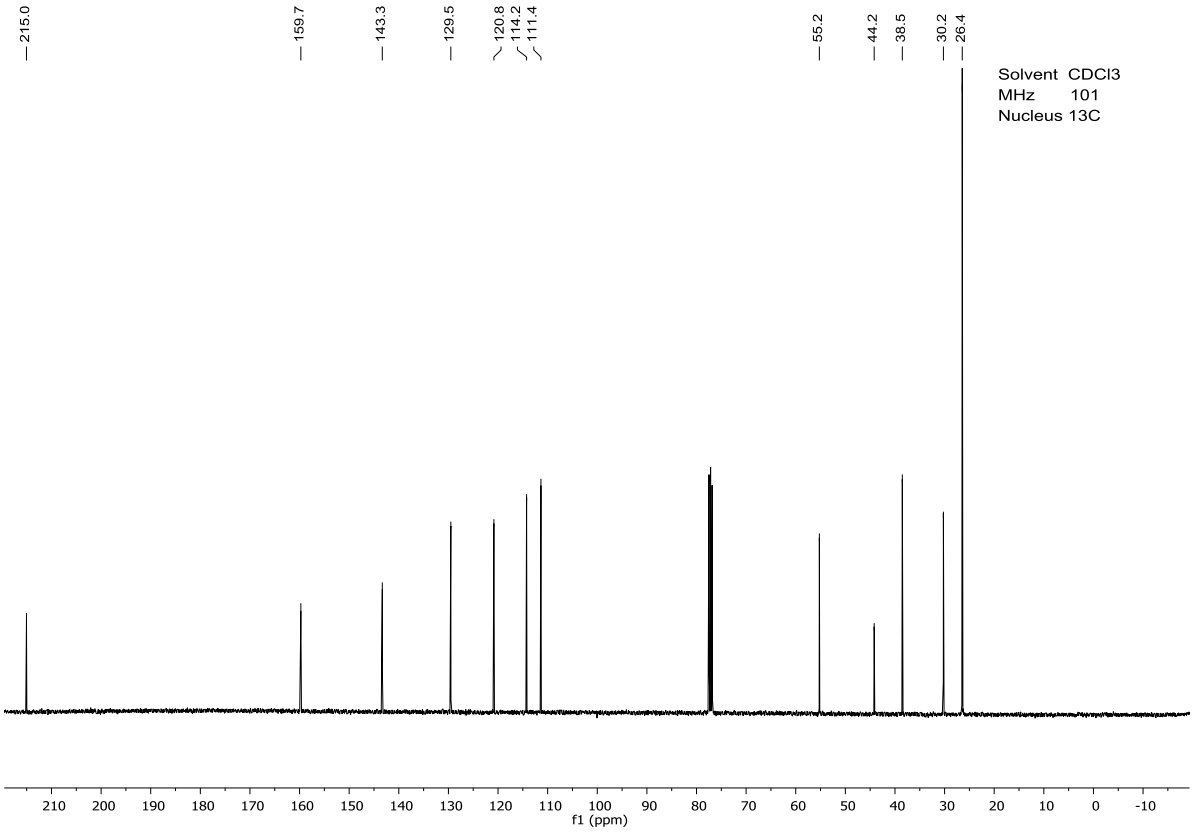

200.4
196.6
158.6
142.4
138.5
137.6
131.3
123.6
116.7
115.0
54.9
53.8
40.7
26.4
25.0
20.3
14.6
Solvent C6D6
MHz 101
Nucleus 13C
f1 (ppm)

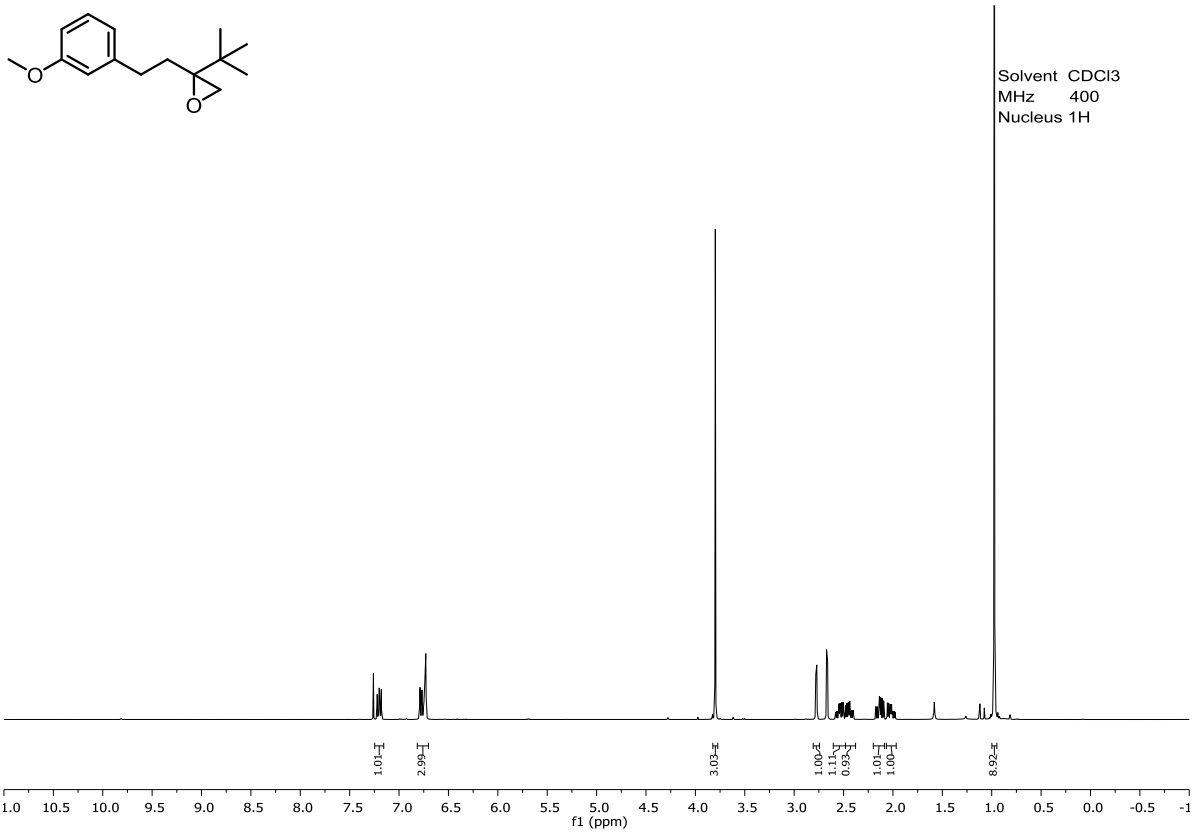

Me
O
H
O
O
H
OH

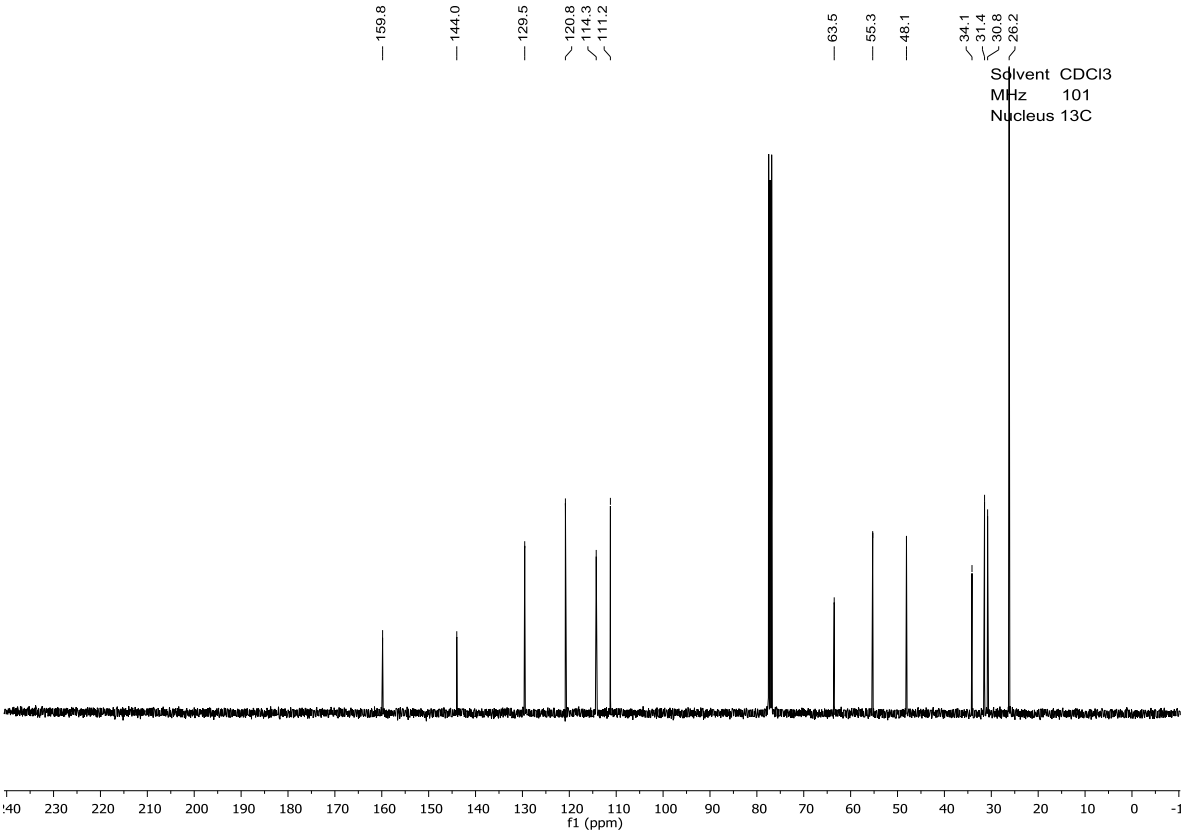
Solvent CDCl3
MHz 400
Nucleus 1H
1.01
1.03
1.00
2.97
2.02
1.01
1.31
1.02
3.17
2.94
3.09
f1 (ppm)

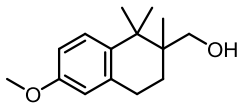

179.5
158.5
137.9
136.7
125.6
113.7
112.2
102.6
55.3
51.3
50.7
43.3
38.4
27.8
25.7
20.4
19.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

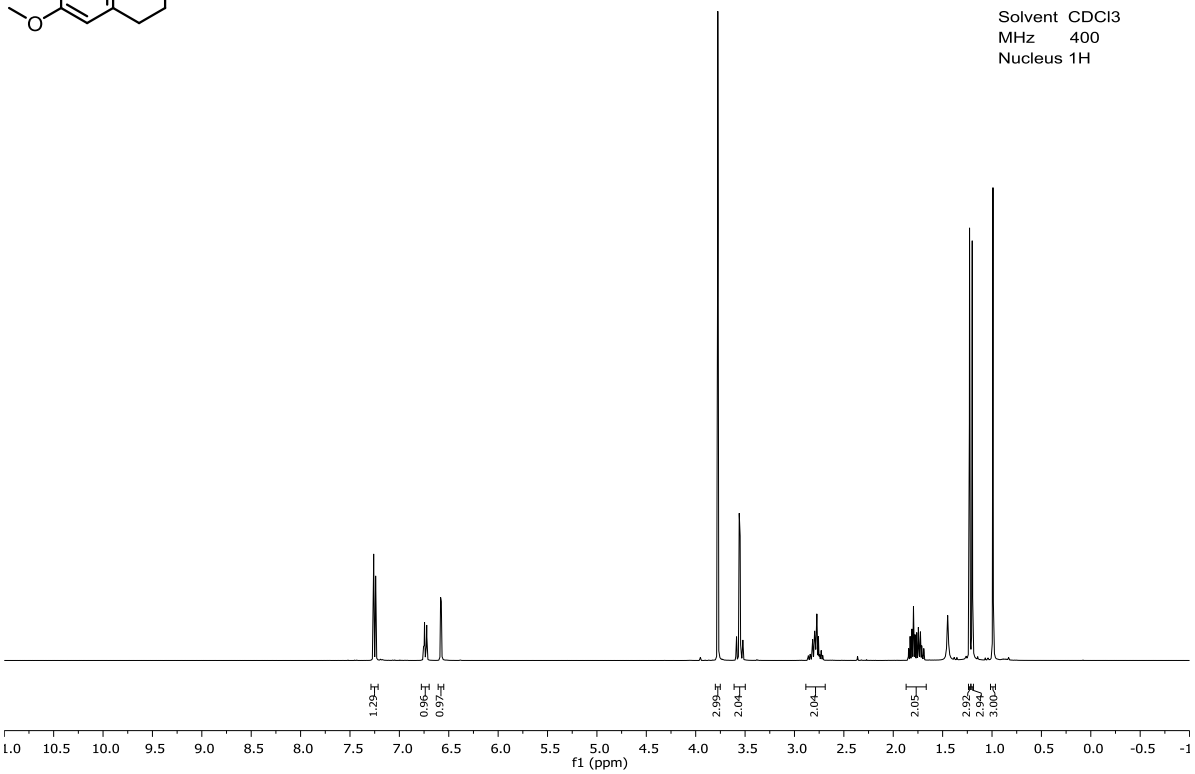

Solvent CDCl3
MHz 400
Nucleus 1H
0.96
2.90
3.00
4.04
8.96
f1 (ppm)

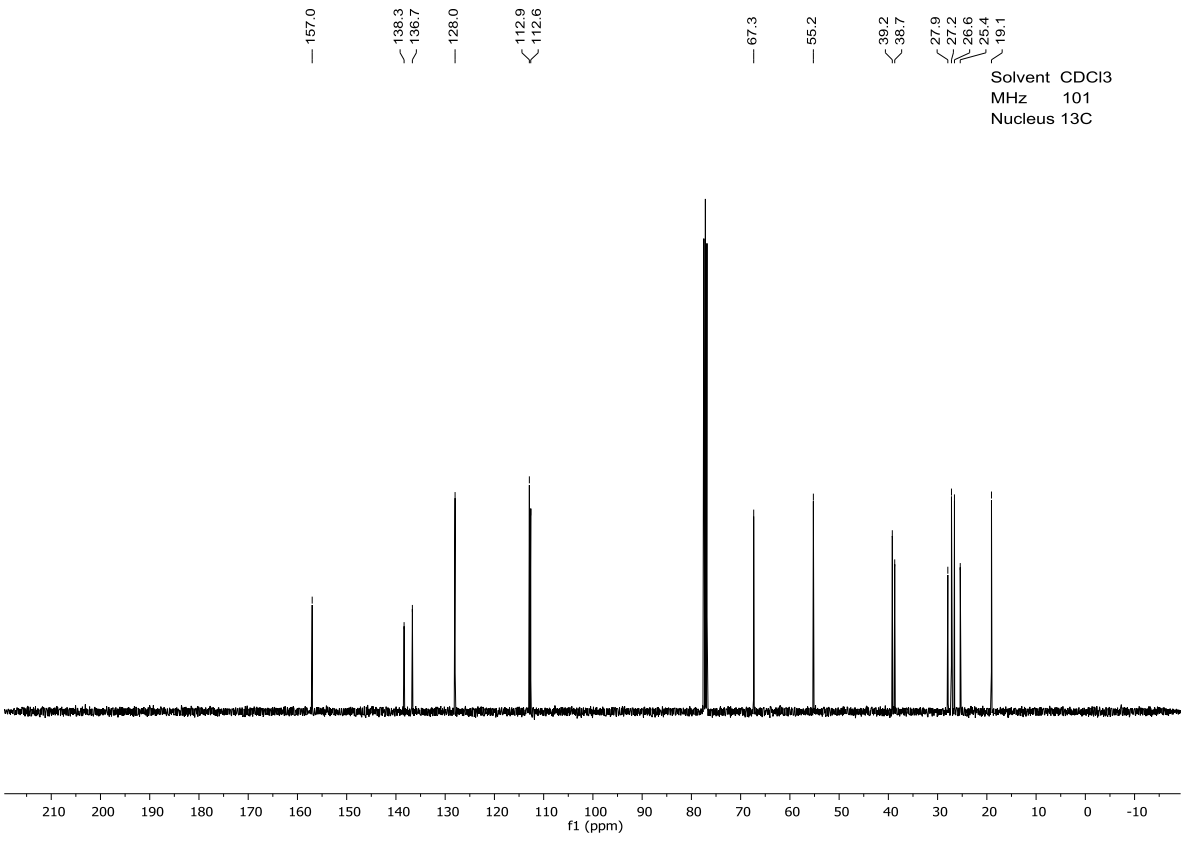

215.0
159.7
143.3
129.5
120.8
114.2
111.4
55.2
44.2
38.5
30.2
26.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

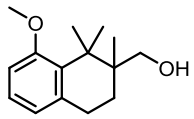

Solvent CDCl3
MHz 400
Nucleus 1H
1.01
2.99
3.03
1.00
1.11
0.93
1.01
1.00
8.92
f1 (ppm)

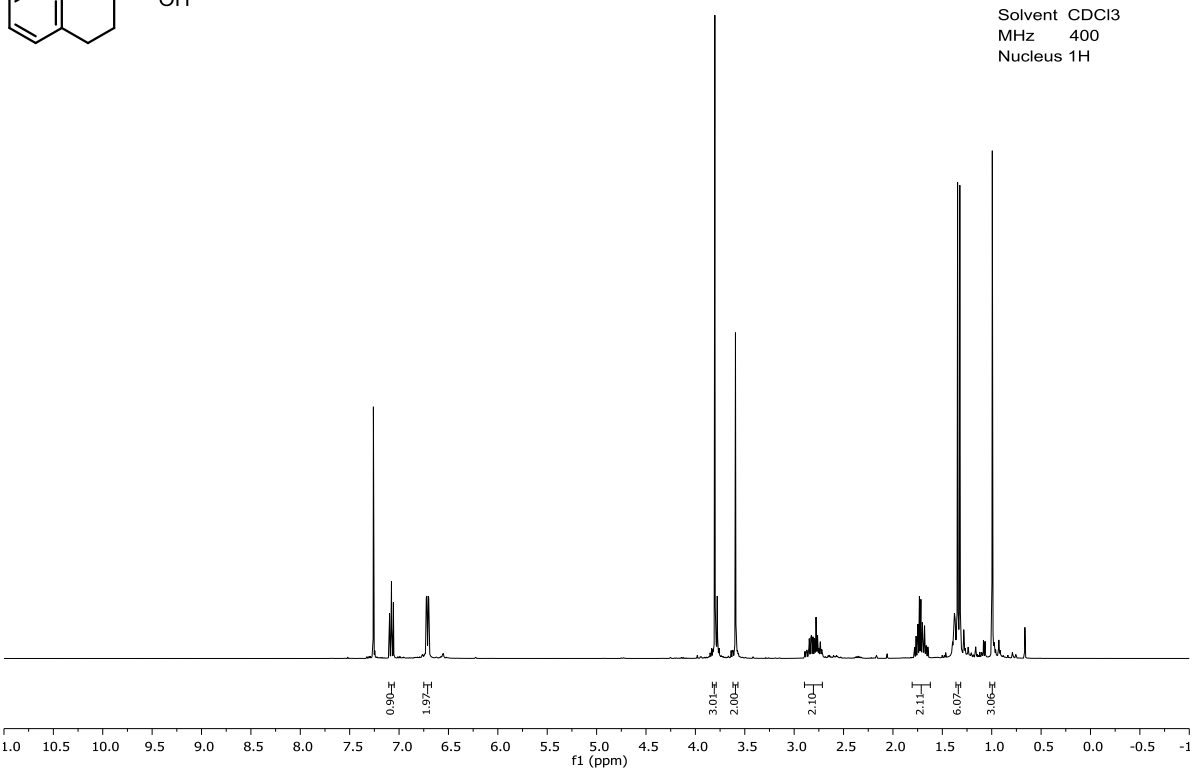

159.8
144.0
129.5
120.8
114.3
111.2
63.5
55.3
48.1
34.1
31.4
30.8
26.2
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

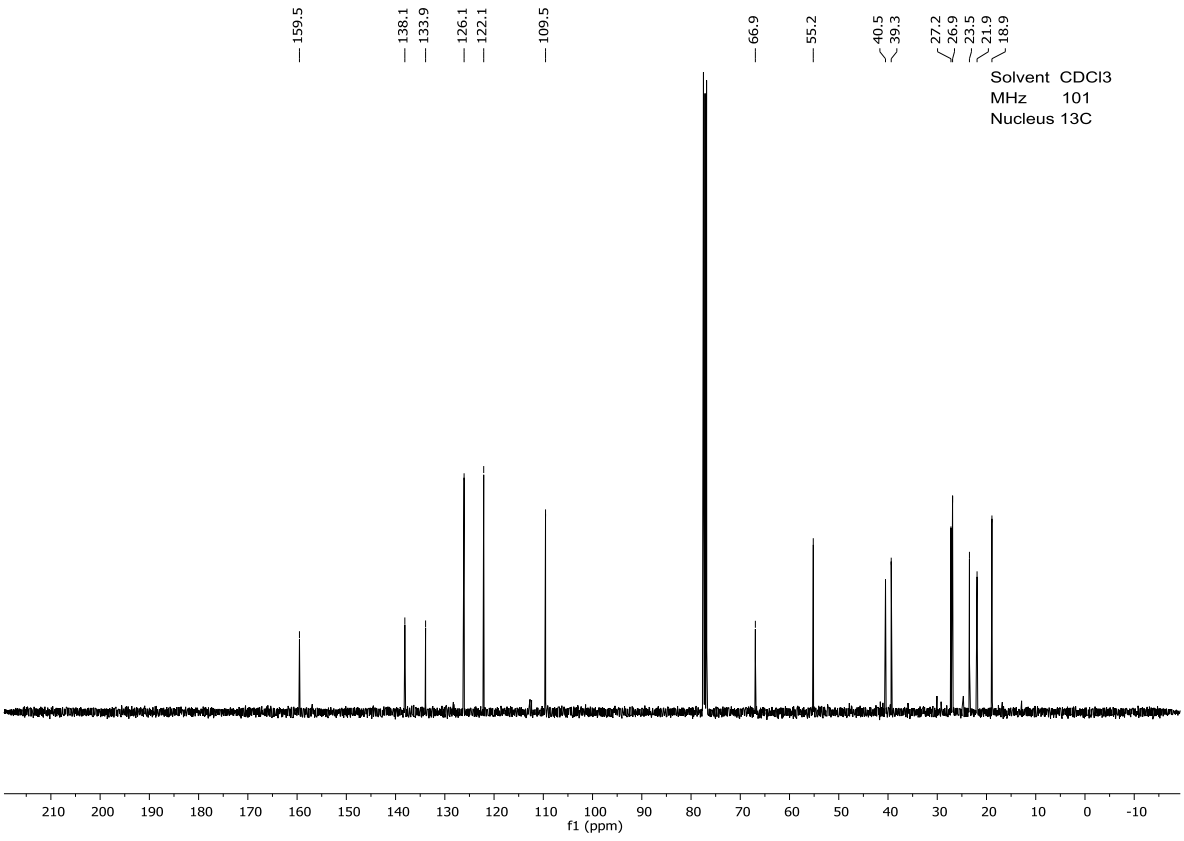

OH
O

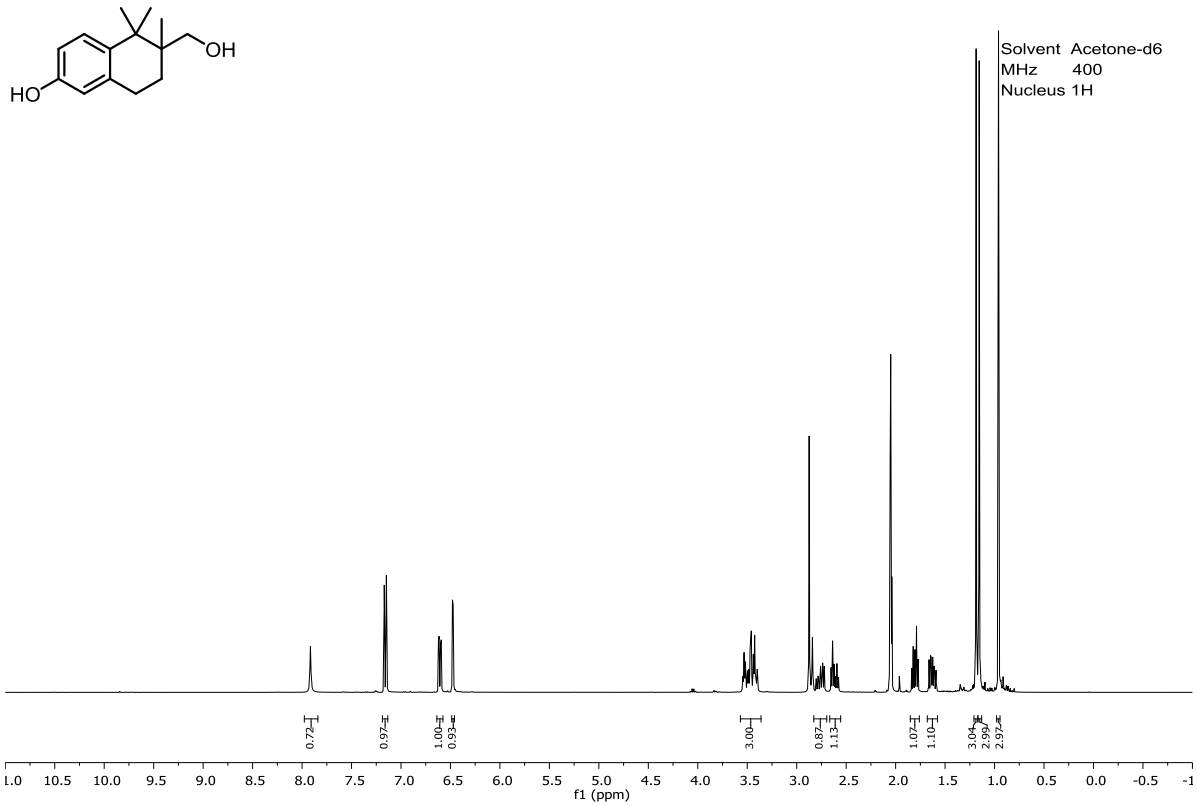

Solvent CDCl3
MHz 400
Nucleus 1H
1.29
0.96
0.97
2.99
2.04
2.04
2.05
2.92
2.94
3.00
f1 (ppm)

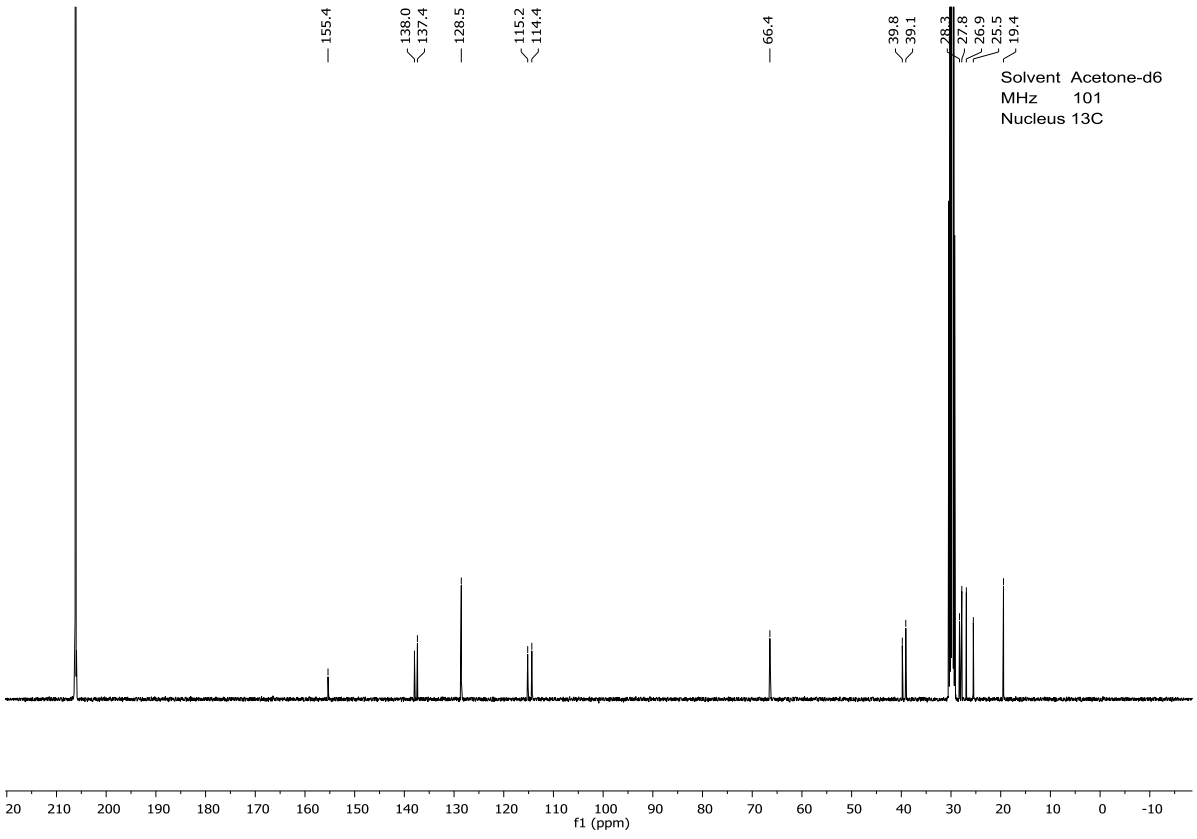

157.0
138.3
136.7
128.0
112.9
112.6
67.3
55.2
39.2
38.7
27.9
27.2
26.6
25.4
19.1
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

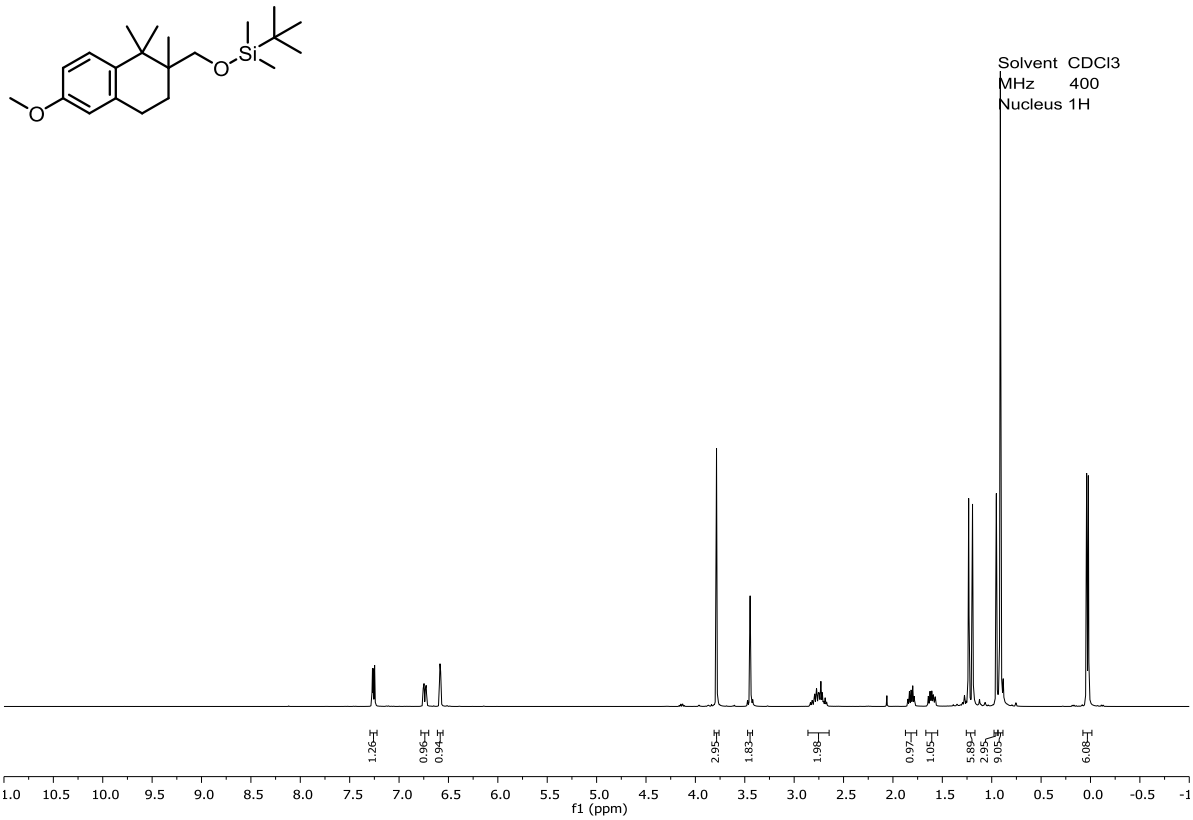

O
OH

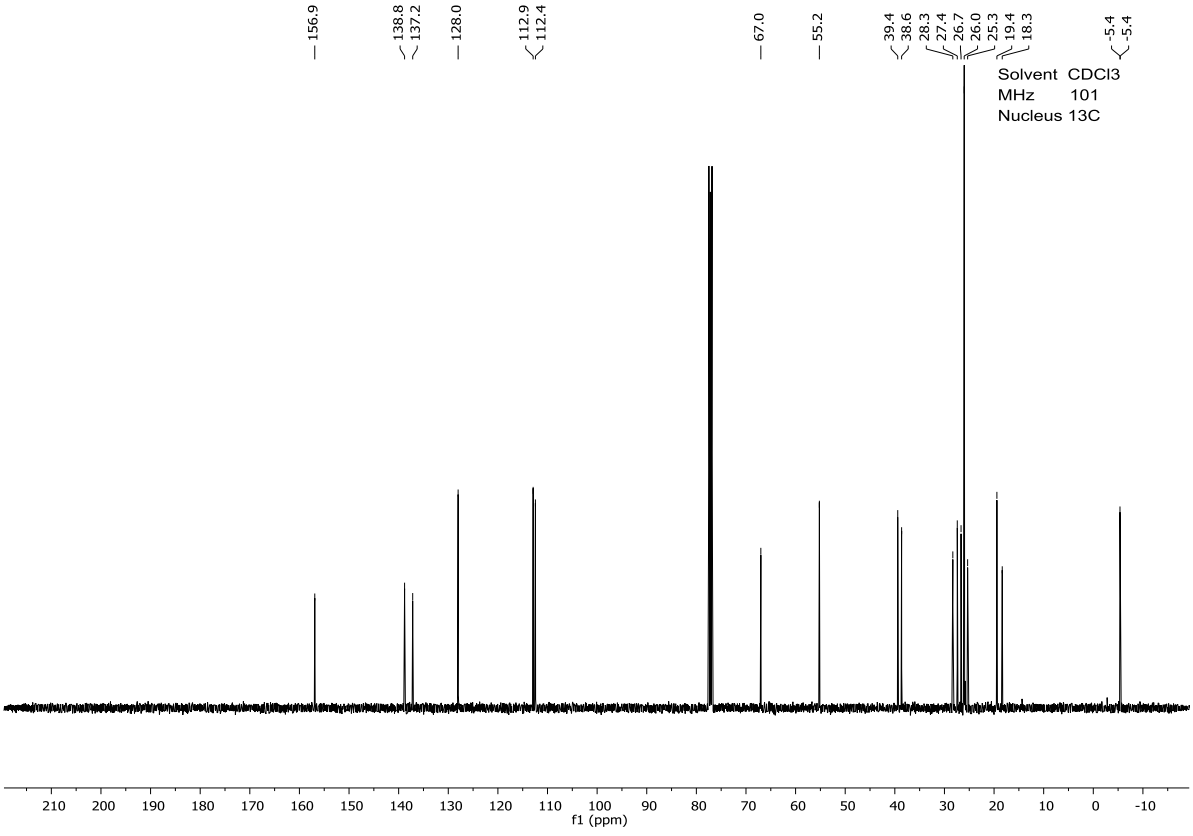

Solvent CDCl3
MHz 400
Nucleus 1H
0.90
1.97
3.01
2.00
2.10
2.11
6.07
3.06
f1 (ppm)

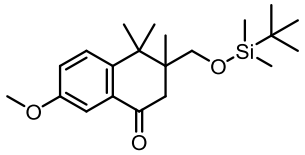

159.5
138.1
133.9
126.1
122.1
109.5
66.9
55.2
40.5
39.3
27.2
26.9
23.5
21.9
18.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


OH
HO
Solvent Acetone-d6
MHz 400
Nucleus 1H
0.72
0.97
1.00
0.93
3.00
0.87
1.13
1.07
1.10
3.04
2.99
2.97
f1 (ppm)

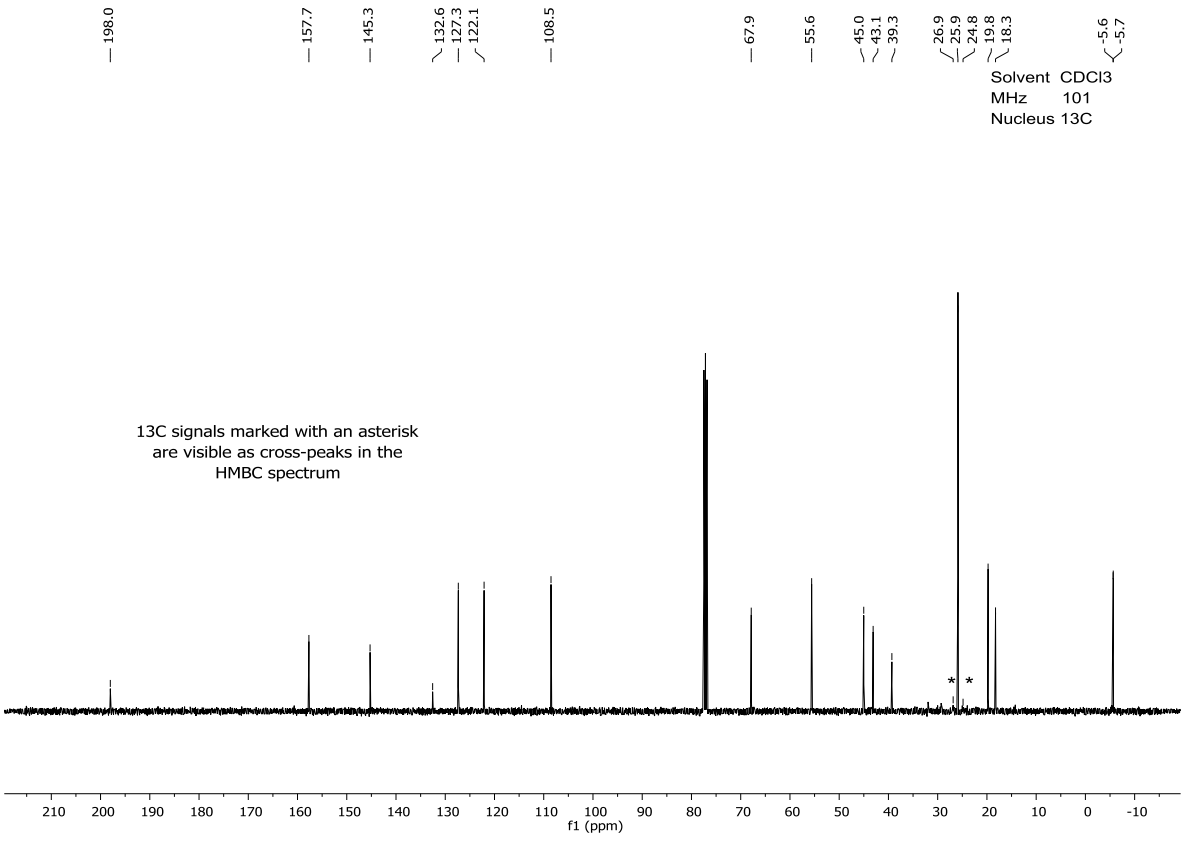

155.4
138.0
137.4
128.5
115.2
114.4
66.4
39.8
39.1
28.3
27.8
26.9
25.5
19.4
Solvent Acetone-d6
MHz 101
Nucleus 13C
f1 (ppm)

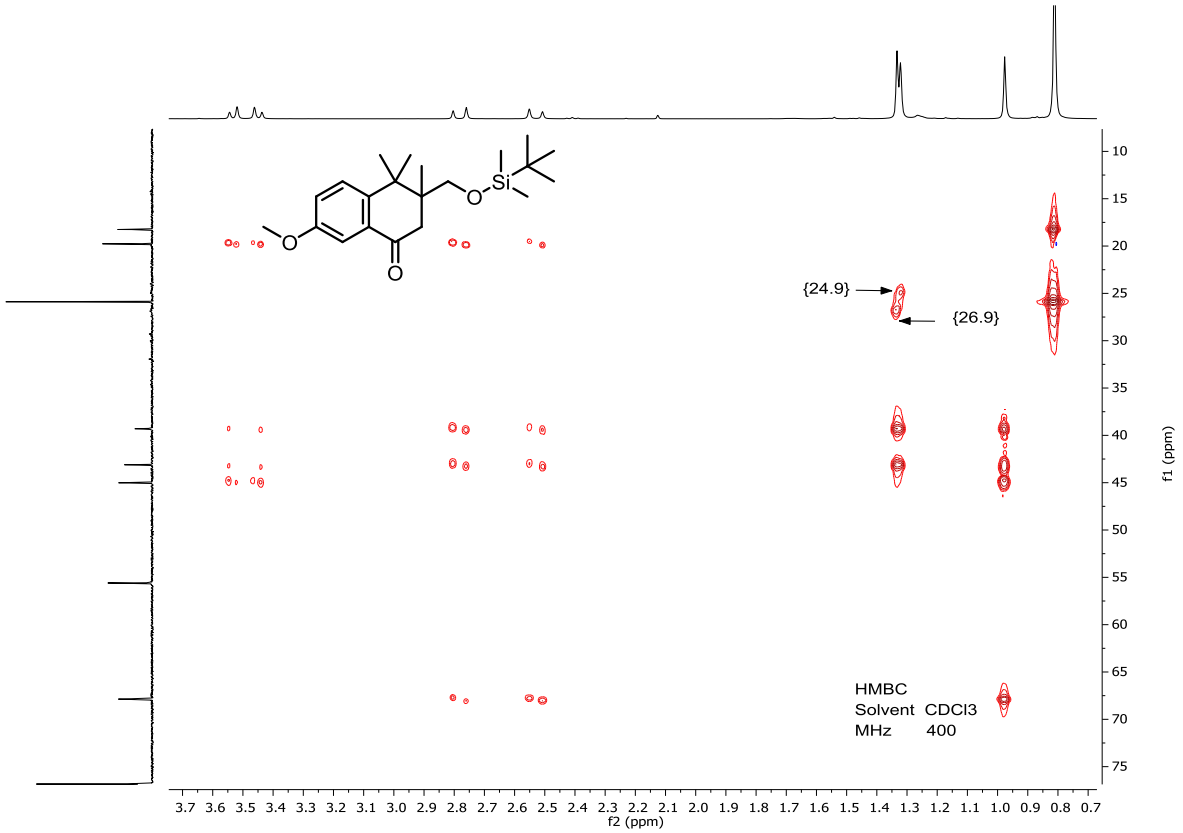

Solvent CDCl3
MHz 400
Nucleus 1H
1.26
0.96
0.94
2.95
1.83
1.98
0.97
1.05
5.89
2.95
9.05
6.08
f1 (ppm)

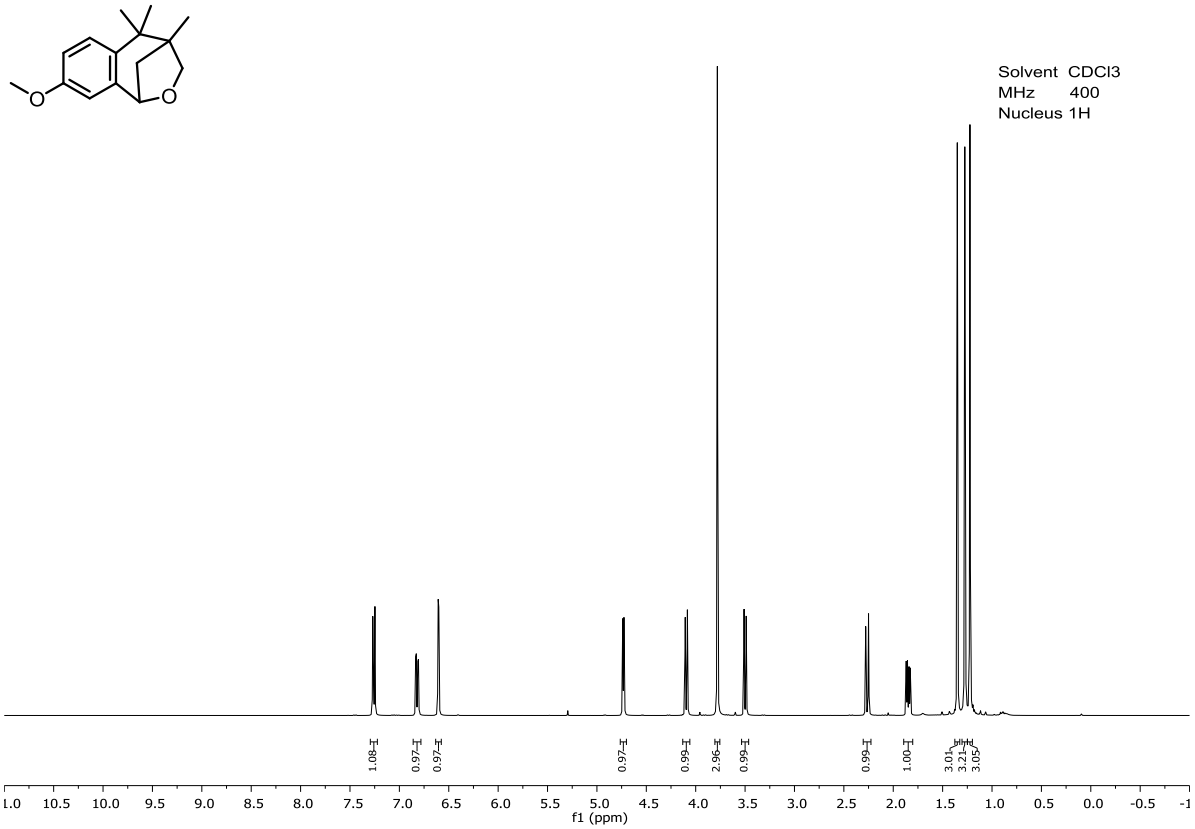

156.9
138.8
137.2
128.0
112.9
112.4
67.0
55.2
39.4
38.6
28.3
27.4
26.7
26.0
25.3
19.4
18.3
-5.4
-5.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

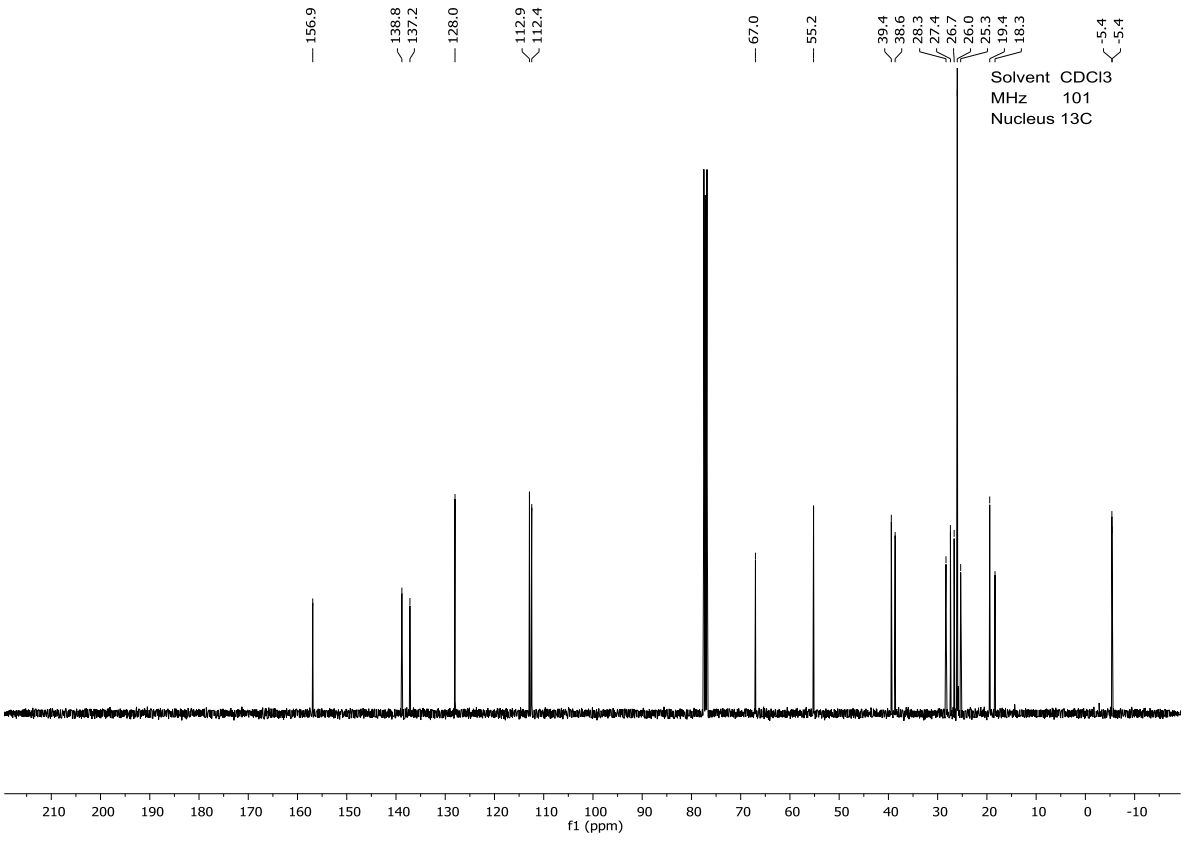

O
Si
O
O

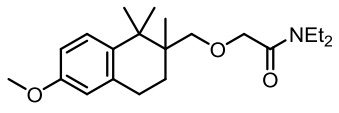
Solvent CDCl3
MHz 400
Nucleus 1H
0.99
1.00
1.01
3.10
1.00
1.01
0.99
0.99
6.12
3.08
9.04
5.95
f1 (ppm)

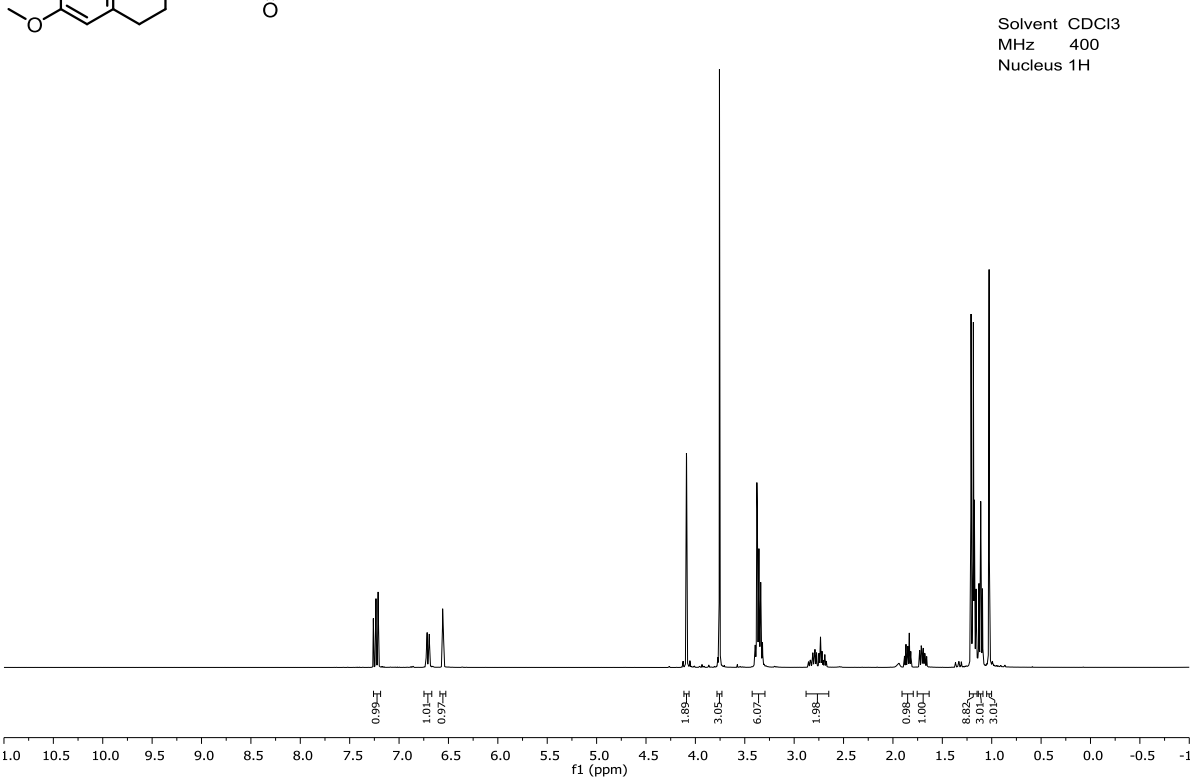

198.0
157.7
145.3
132.6
127.3
122.1
108.5
67.9
55.6
45.0
43.1
39.3
26.9
25.9
24.8
19.8
18.3
-5.6
-5.7
Solvent CDCl3
MHz 101
Nucleus 13C
13C signals marked with an asterisk
are visible as cross-peaks in the
HMBC spectrum
f1 (ppm)

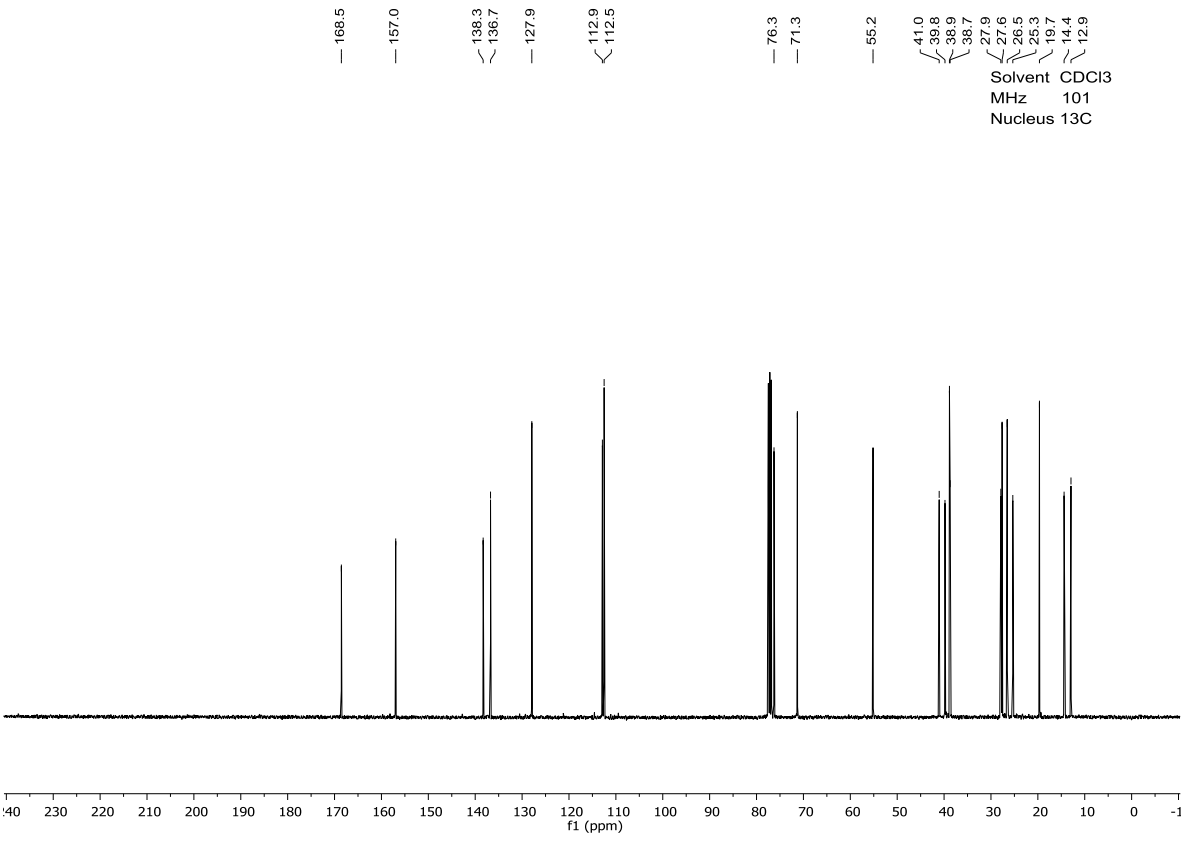

{24.9}
{26.9}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)


Solvent CDCl3
MHz 400
Nucleus 1H
1.08
0.97
0.97
0.97
0.99
2.96
0.99
0.99
1.00
3.01
3.21
3.05
f1 (ppm)

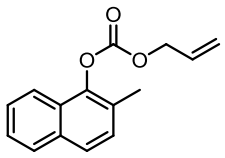

156.9
138.8
137.2
128.0
112.9
112.4
67.0
55.2
39.4
38.6
28.3
27.4
26.7
26.0
25.3
19.4
18.3
-5.4
-5.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

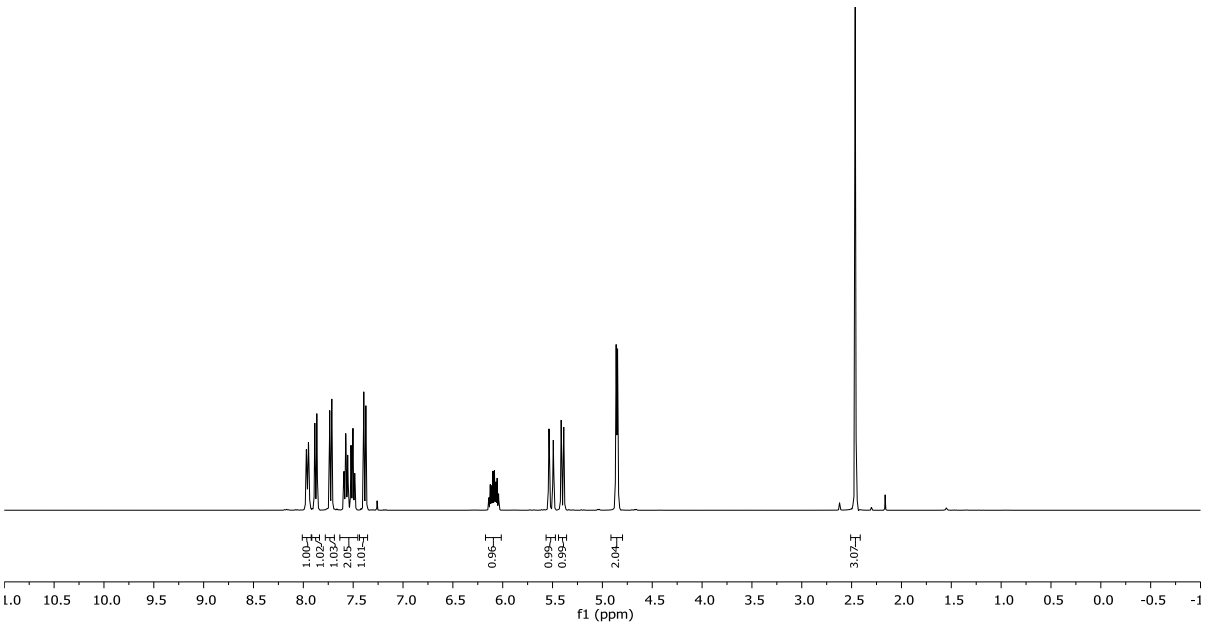

NEt2
O
O
O

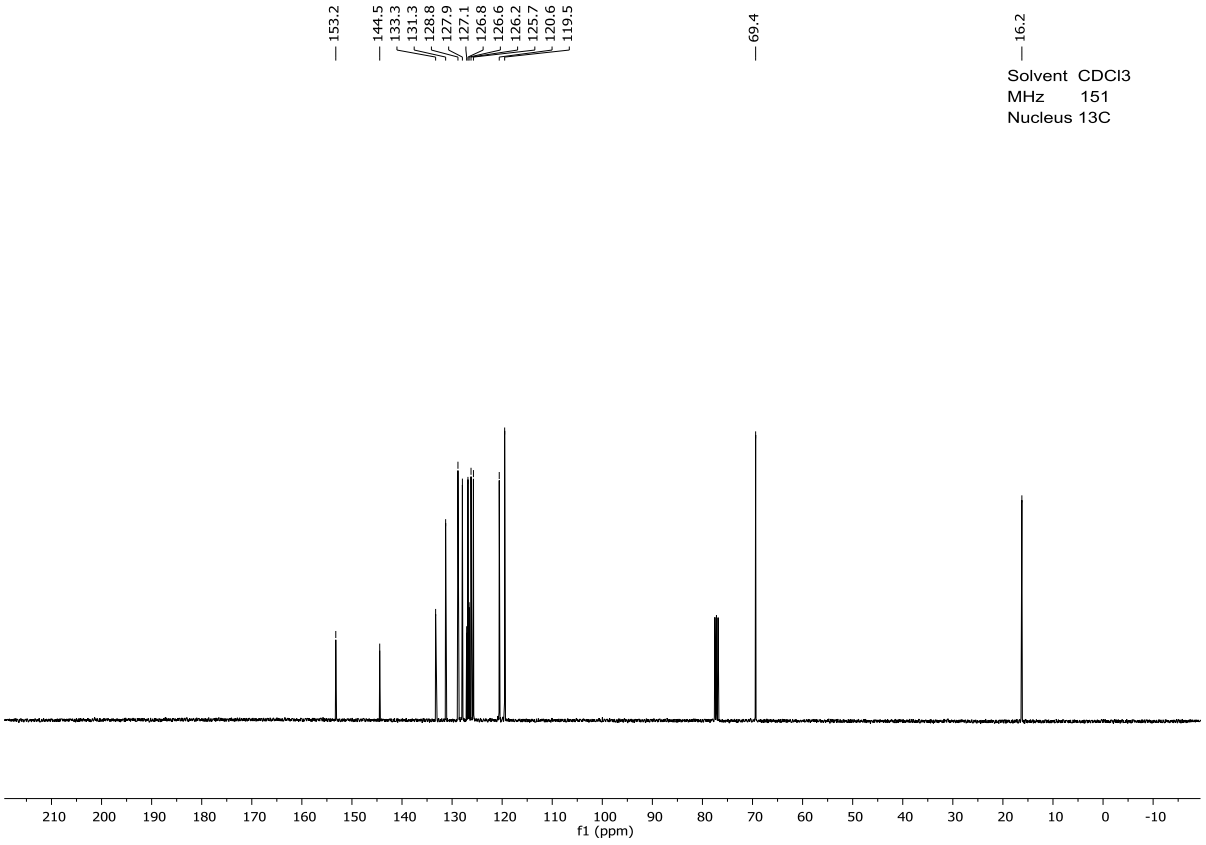

Solvent CDCl3
MHz 400
Nucleus 1H
0.99
1.01
0.97
1.89
3.05
6.07
1.98
0.98
1.00
8.82
3.01
3.01
f1 (ppm)

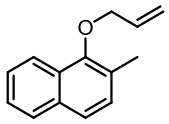

168.5
157.0
138.3
136.7
127.9
112.9
112.5
76.3
71.3
55.2
41.0
39.8
38.9
38.7
27.9
27.6
26.5
25.3
19.7
14.4
12.9
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

11.3 NMR Spectra of Chapter II

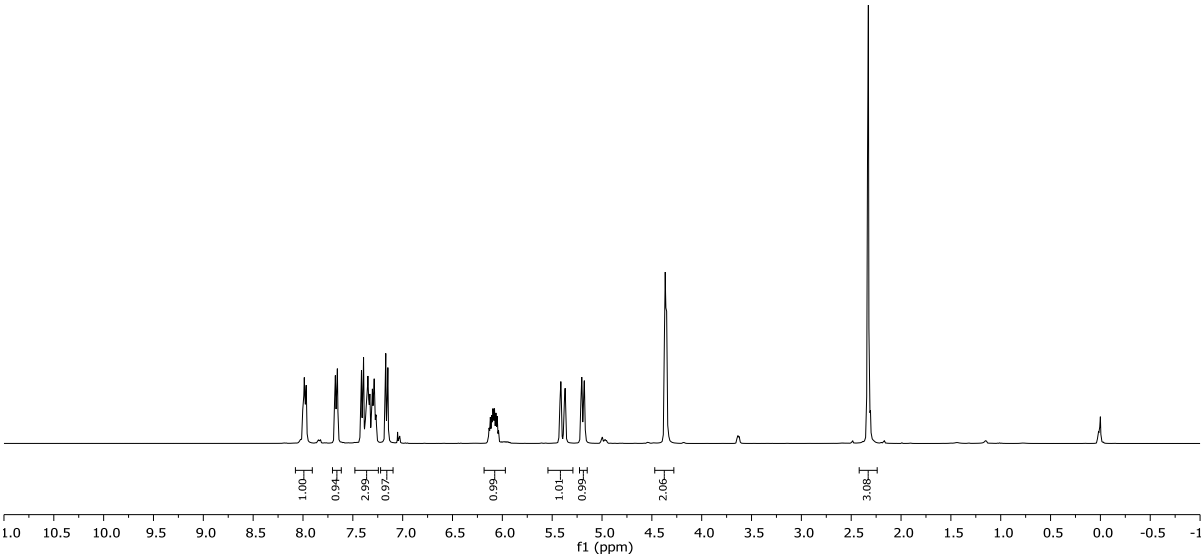






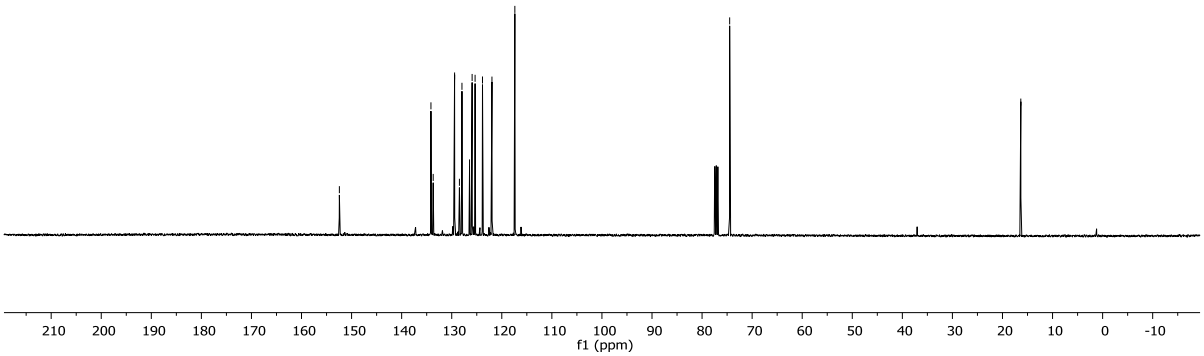


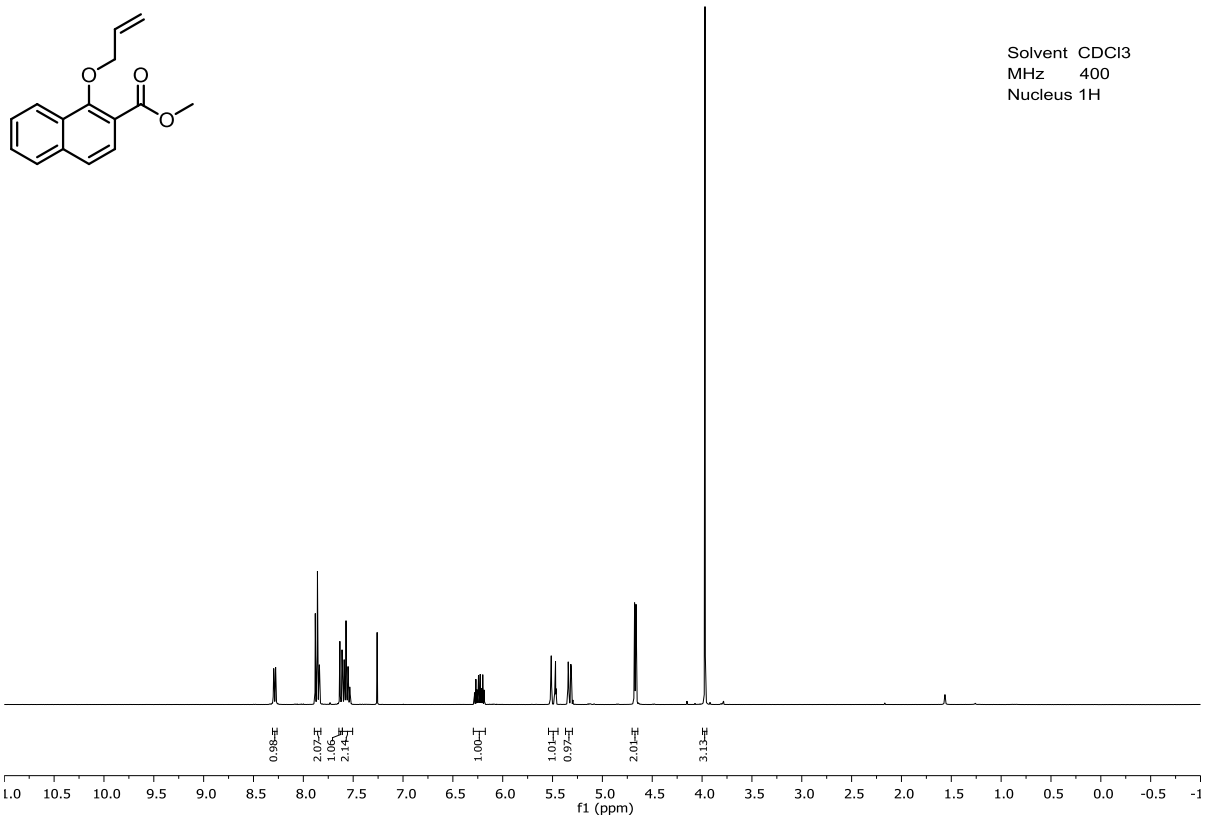
Solvent CDCl3
MHz 599
Nucleus 1H

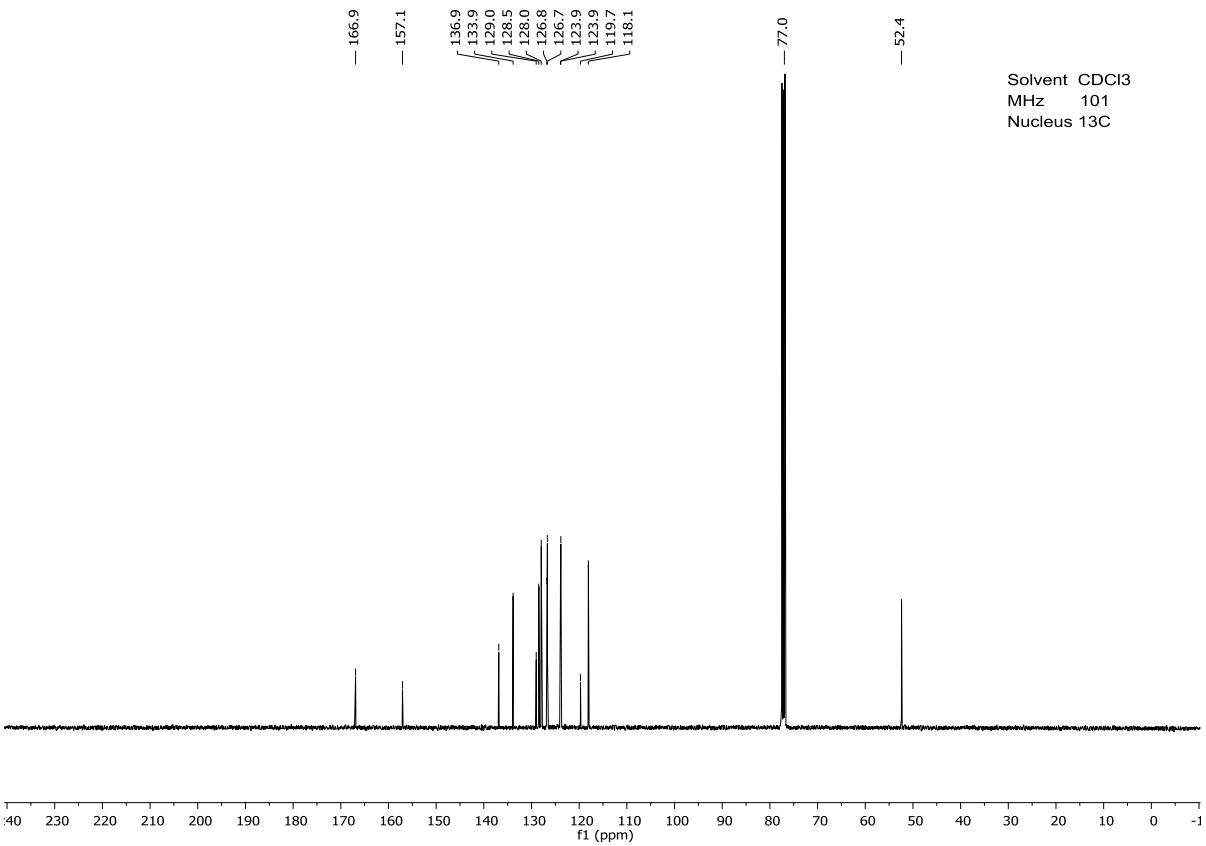


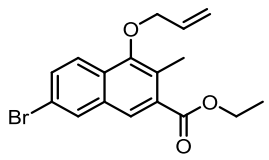
152.4
134.2
133.7
129.4
128.5
128.0
126.4
125.9
125.3
123.9
122.0
117.4
74.5
16.3

Solvent CDCl3
MHz 151
Nucleus 13C

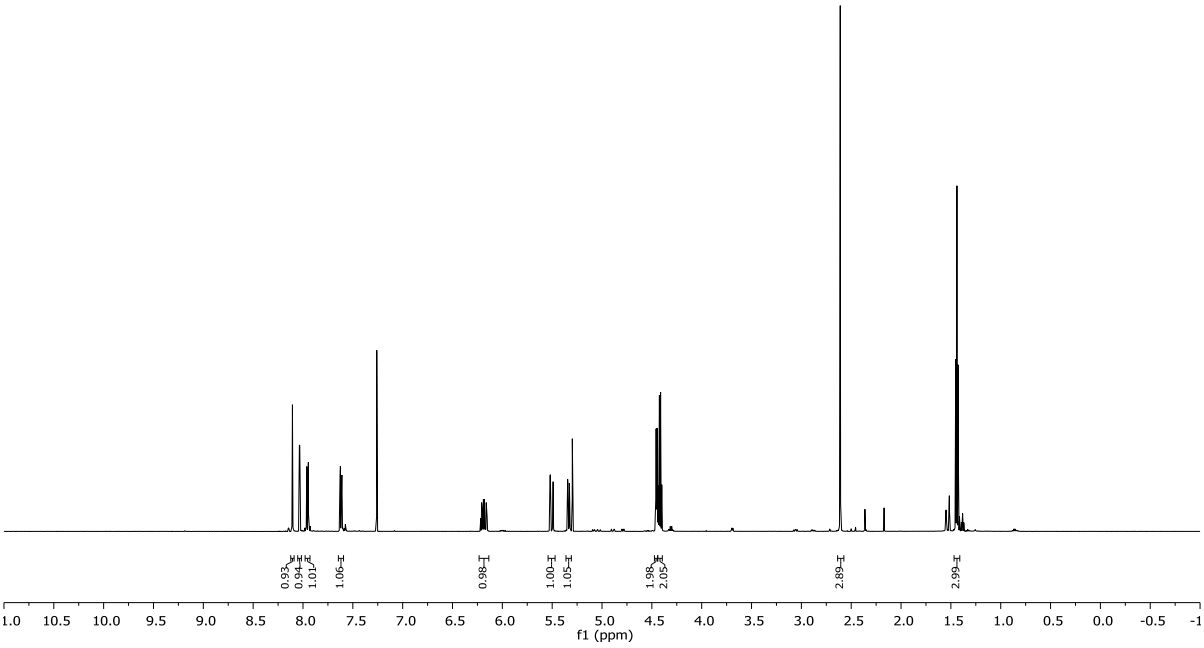


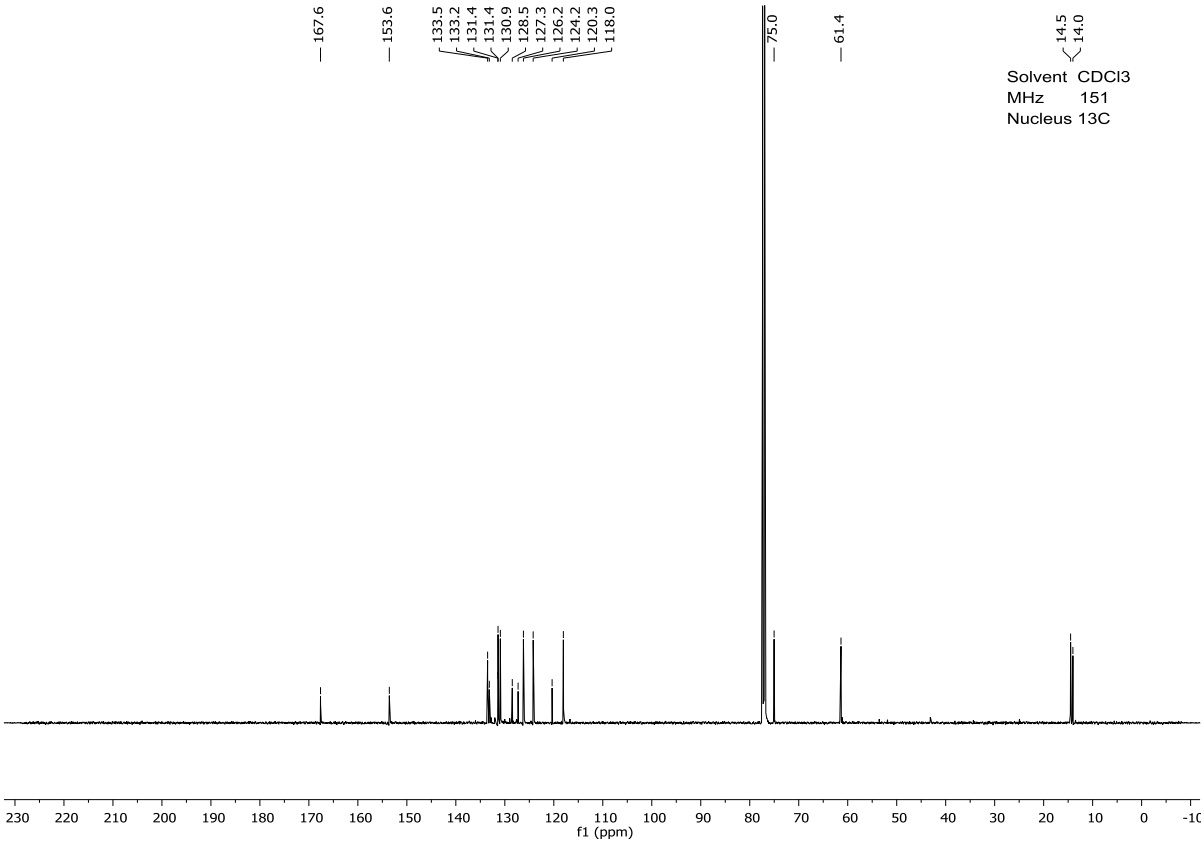

Solvent CDCl3
MHz 400
Nucleus 1H
0.98
2.07
1.06
2.14
1.00
1.01
0.97
2.01
3.13
f1 (ppm)


166.9
157.1
136.9
133.9
129.0
128.5
128.0
126.8
126.7
123.9
123.9
119.7
118.1
77.0
52.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

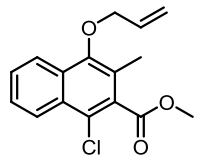


Solvent CDCl3
MHz 599
Nucleus 1H

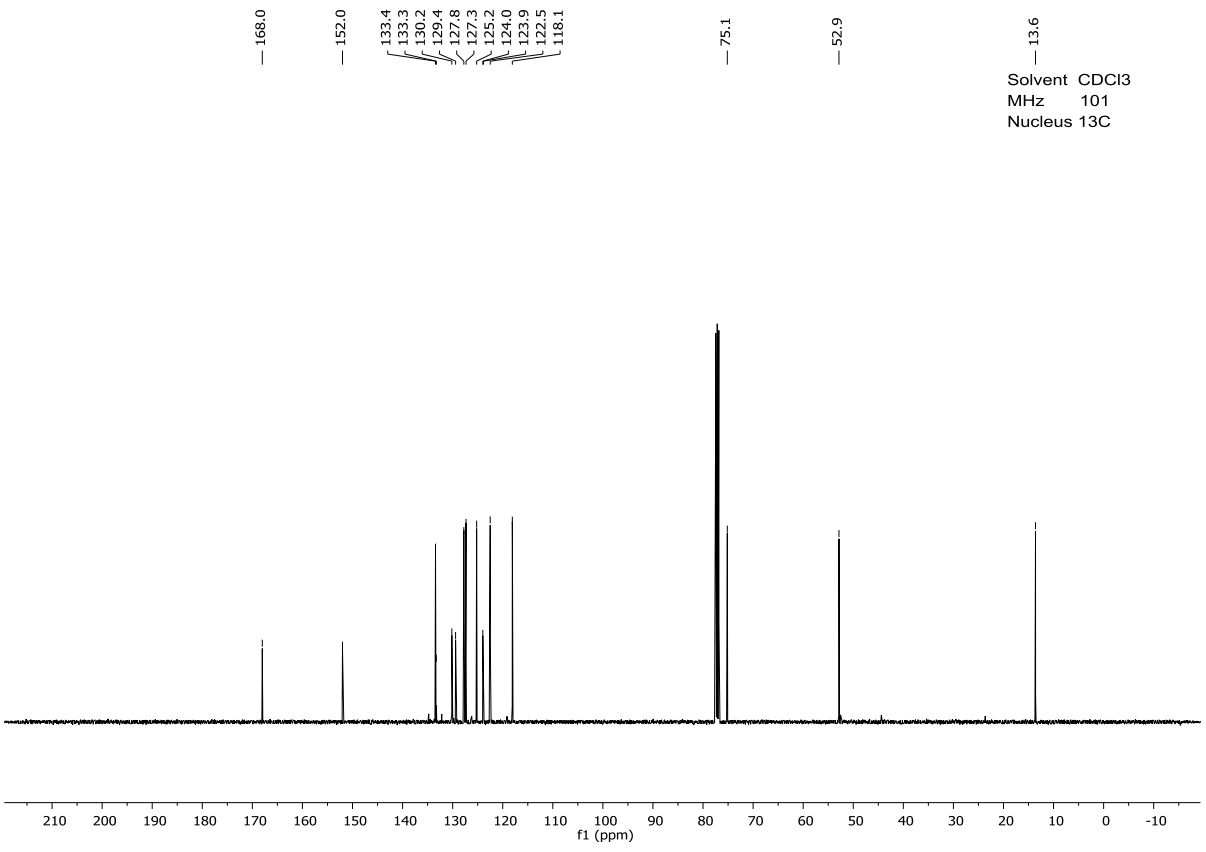


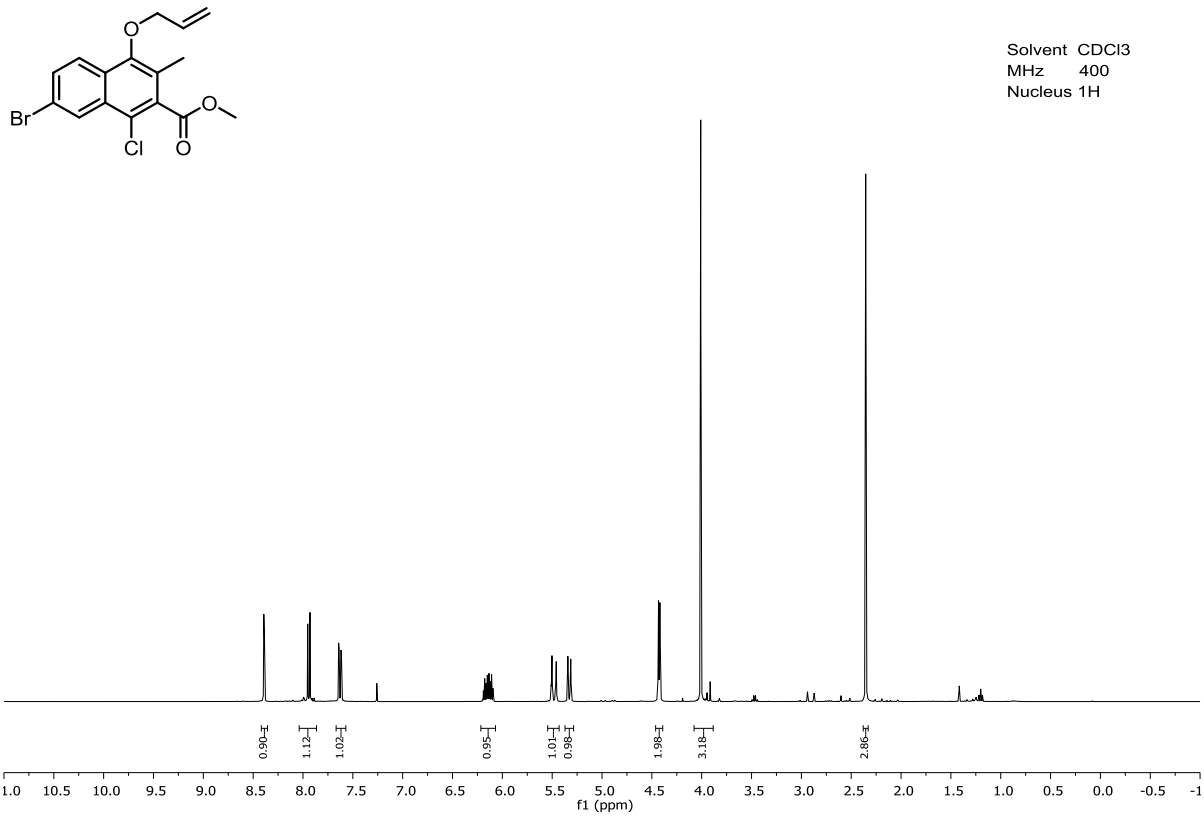


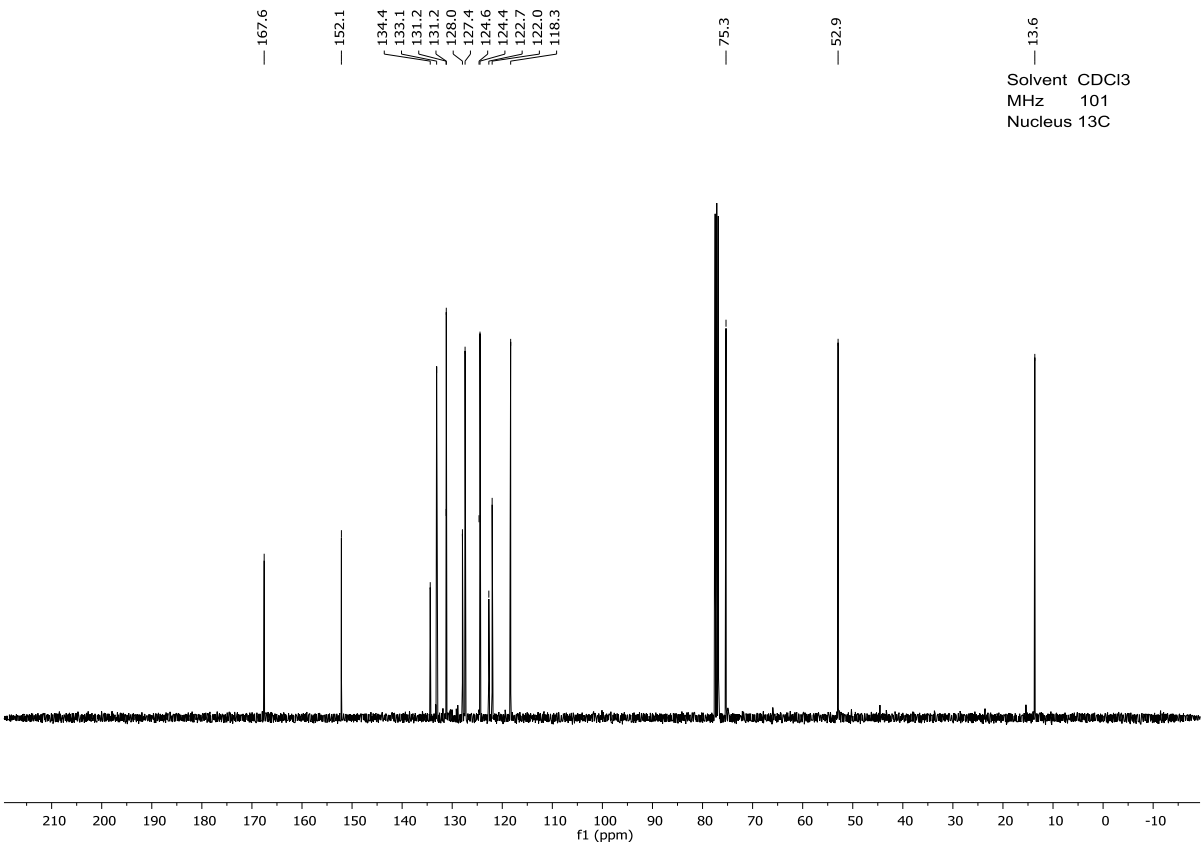
Solvent CDCl3
MHz 151
Nucleus 13C

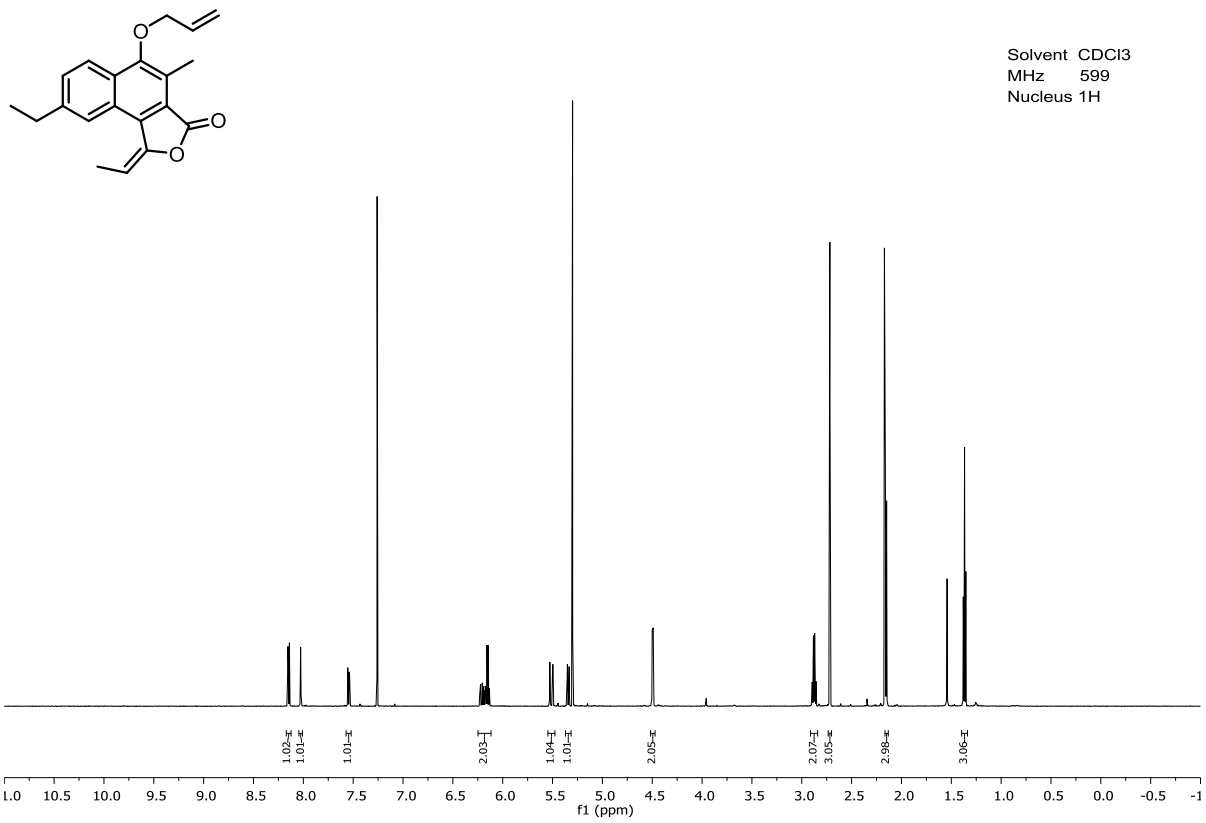

O
O
Cl
O

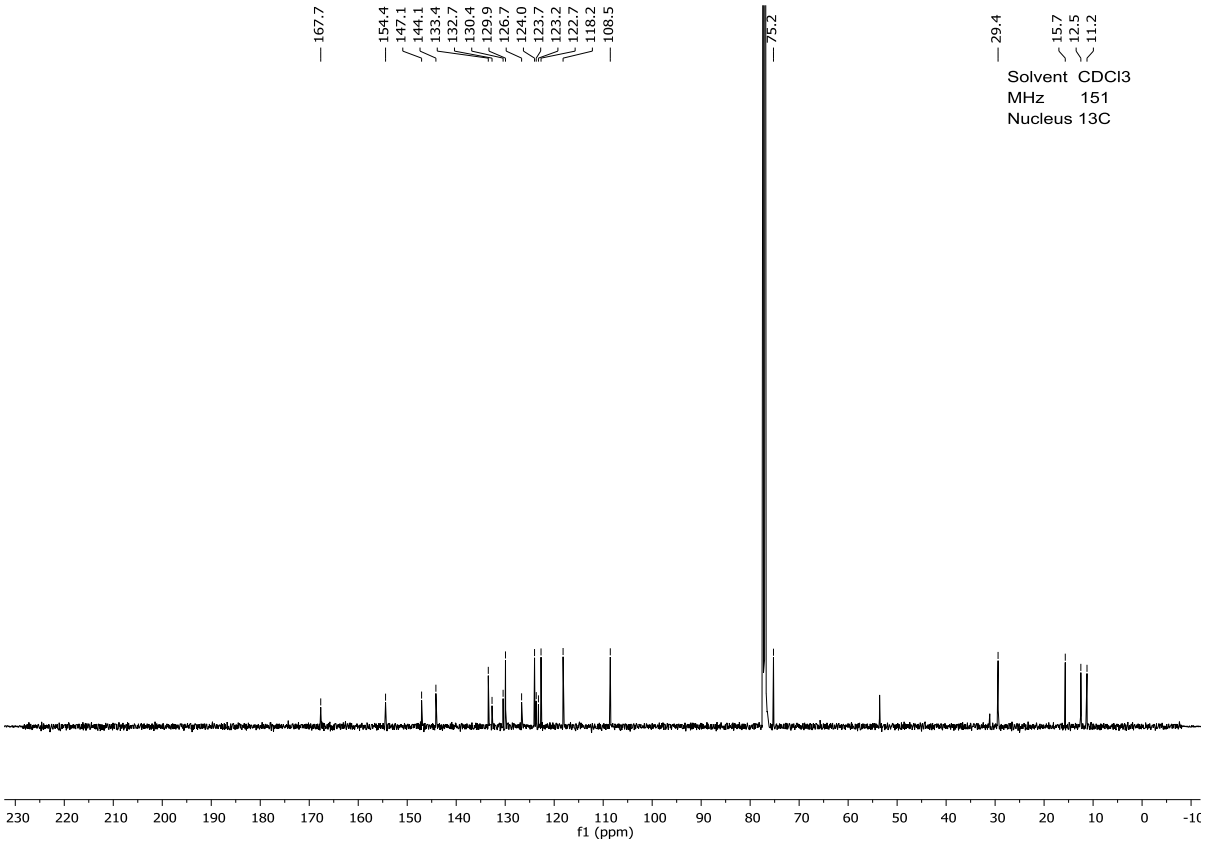
Solvent CDCl3
MHz 400
Nucleus 1H
0.98
1.04
2.01
0.96
1.03
0.99
2.02
2.98
2.99
f1 (ppm)

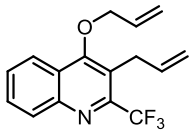

168.0
152.0
133.4
133.3
130.2
129.4
127.8
127.3
125.2
124.0
123.9
122.5
118.1
75.1
52.9
13.6
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


Br
Cl
O
O
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.90
1.12
1.02
0.95
1.01
0.98
1.98
3.18
2.86
f1 (ppm)

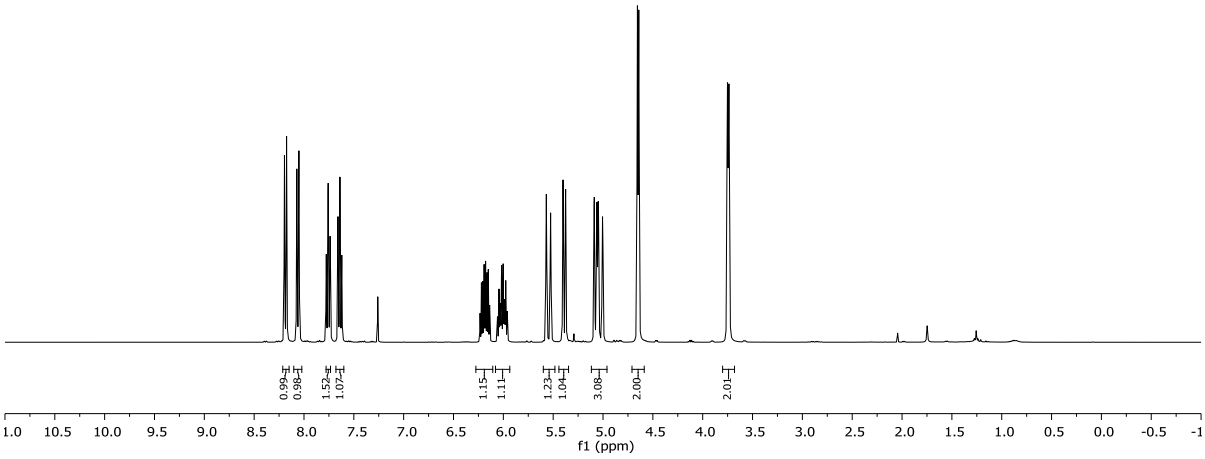

167.6
152.1
134.4
133.1
131.2
131.2
128.0
127.4
124.6
124.4
122.7
122.0
118.3
75.3
52.9
13.6
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

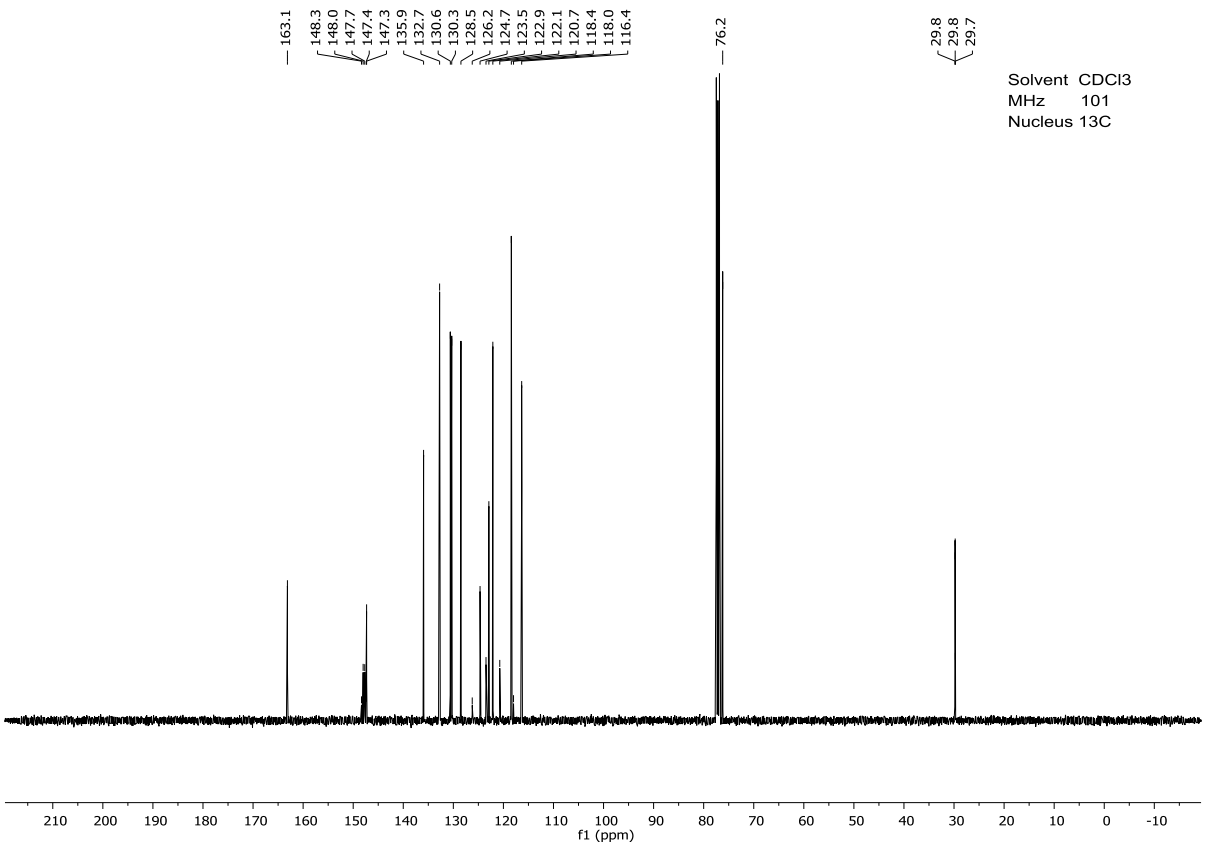

Solvent CDCl3
MHz 599
Nucleus 1H
1.02
1.01
1.01
2.03
1.04
1.01
2.05
2.07
3.05
2.98
3.06
f1 (ppm)


167.7
154.4
147.1
144.1
133.4
132.7
130.4
129.9
126.7
124.0
123.7
123.2
122.7
118.2
108.5
75.2
29.4
15.7
12.5
11.2
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

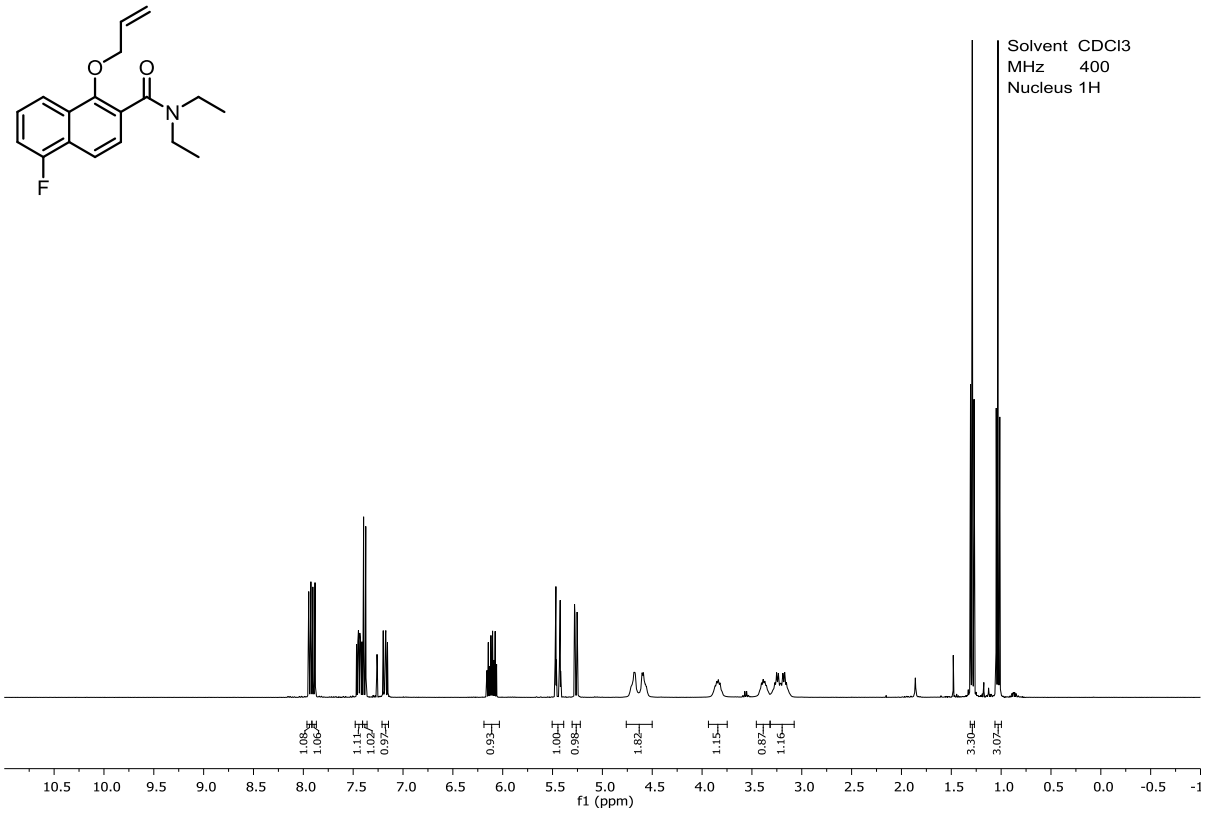


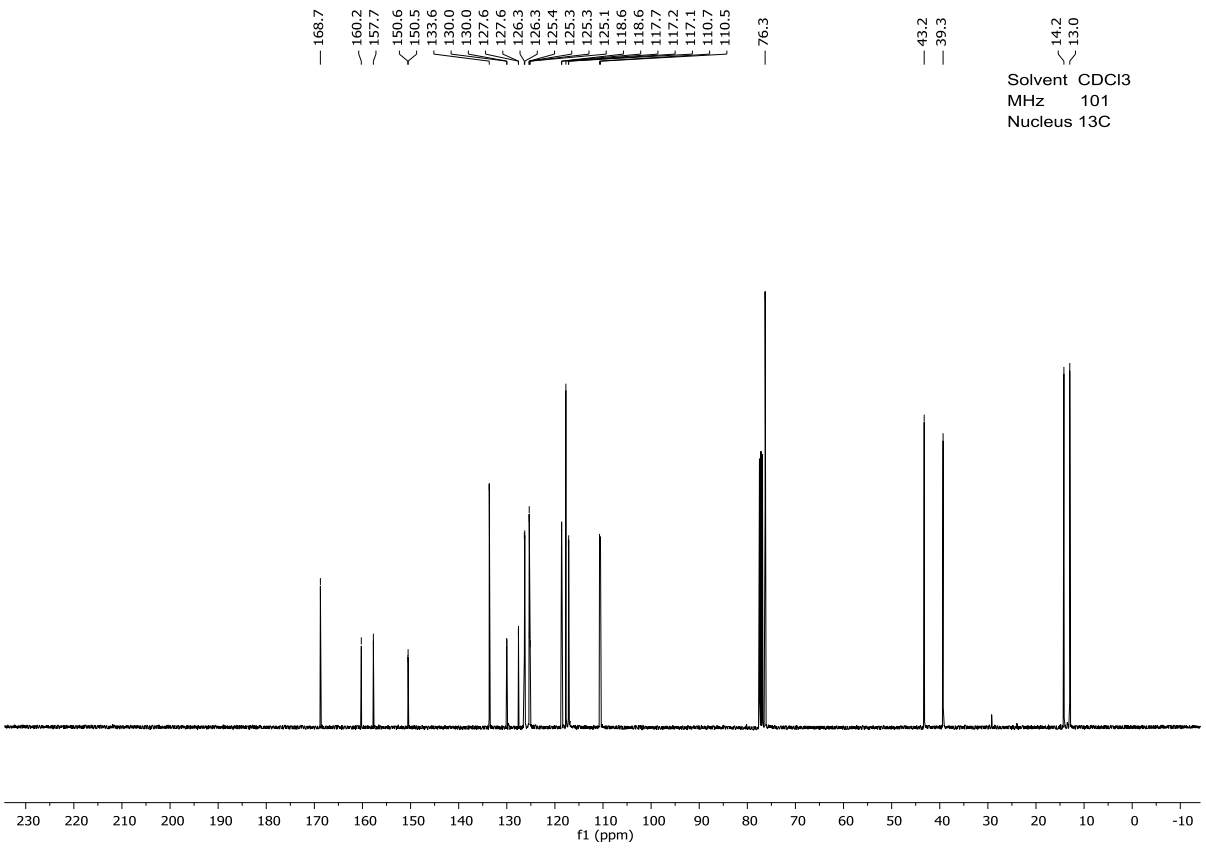
Solvent CDCl3
MHz 400
Nucleus 1H

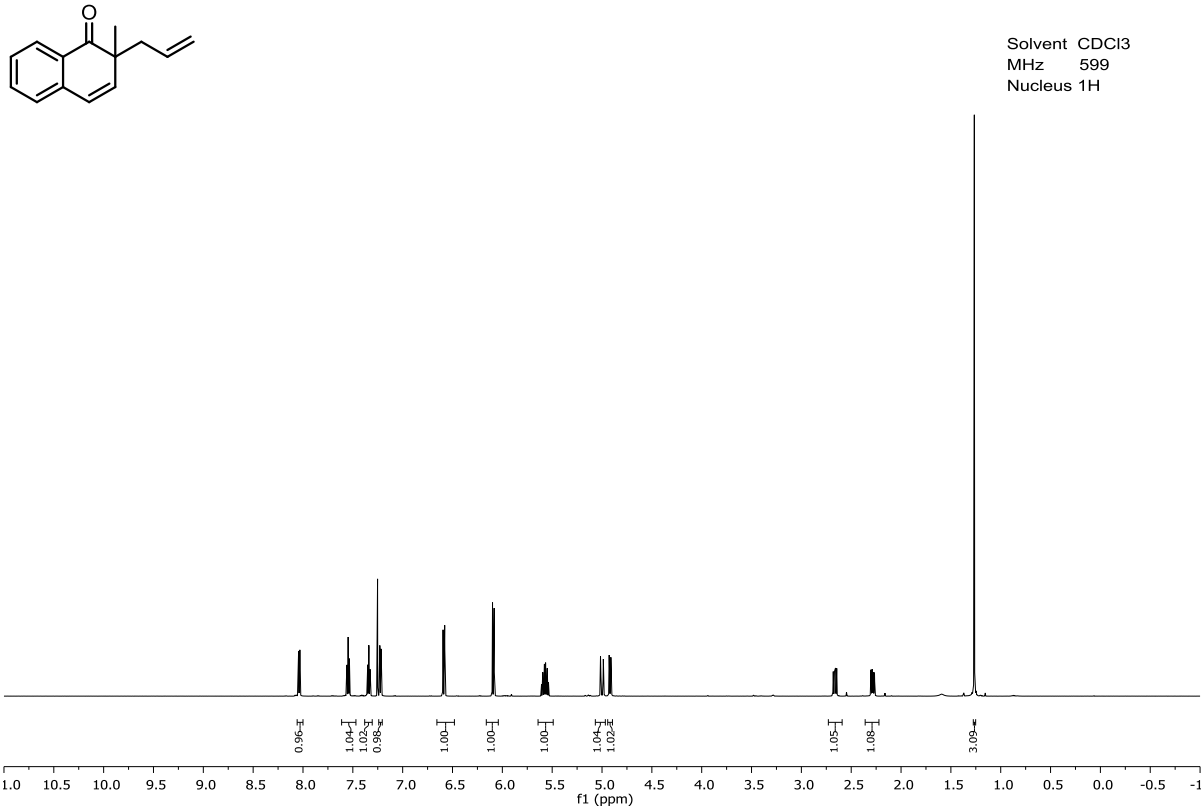


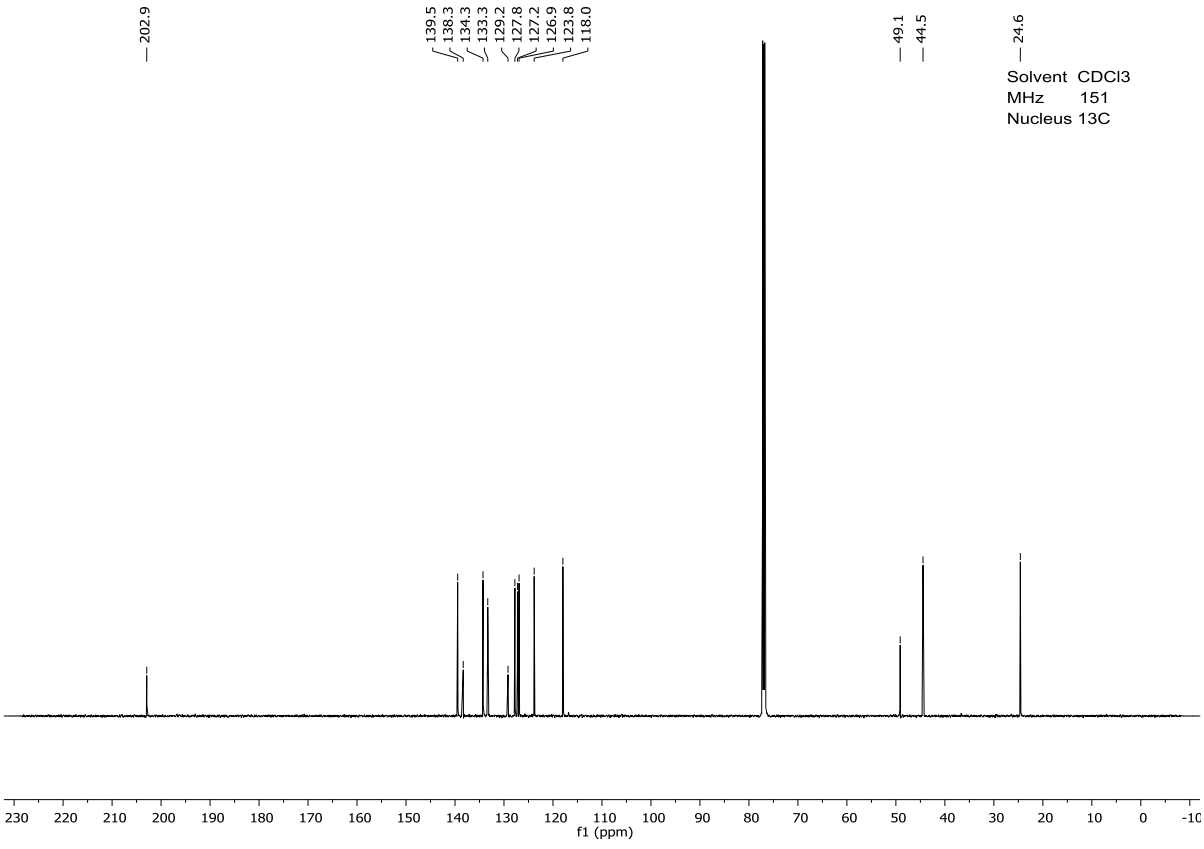


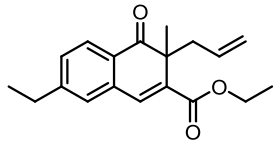
Solvent CDCl3
MHz 101
Nucleus 13C


Solvent CDCl3
MHz 400
Nucleus 1H
1.08
1.06
1.11
1.02
0.97
0.93
1.00
0.98
1.82
1.15
0.87
1.16
3.30
3.07
f1 (ppm)

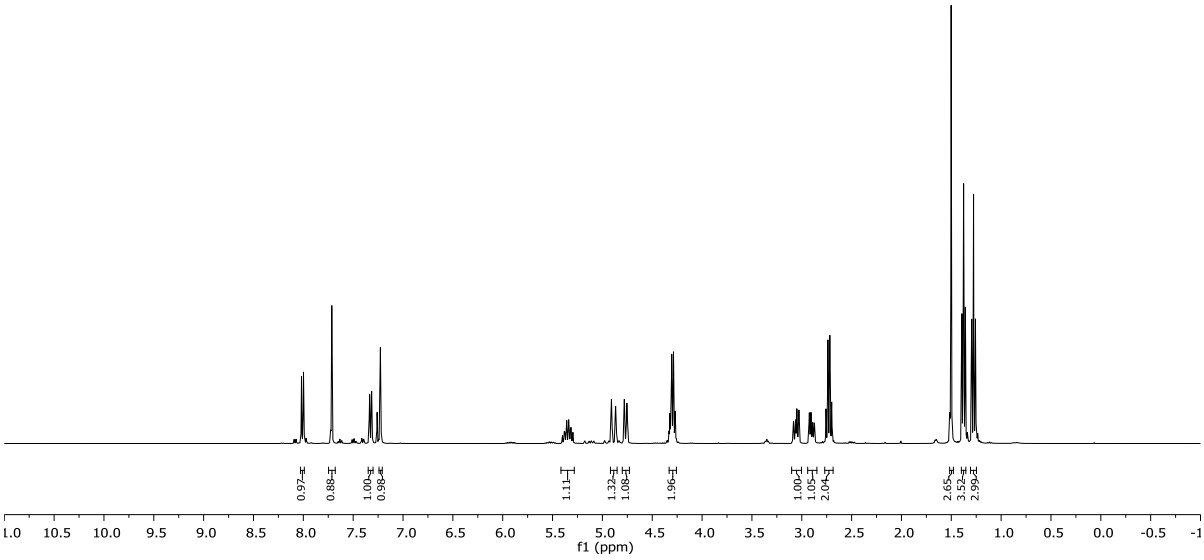

168.7
160.2
157.7
150.6
150.5
133.6
130.0
130.0
127.6
127.6
126.3
126.3
125.4
125.3
125.3
125.1
118.6
118.6
117.7
117.2
117.1
110.7
110.5
76.3
43.2
39.3
14.2
13.0
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)


Solvent CDCl3
MHz 599
Nucleus 1H
0.96
1.04
1.02
0.98
1.00
1.00
1.00
1.04
1.02
1.05
1.08
3.09
f1 (ppm)


202.9
139.5
138.3
134.3
133.3
129.2
127.8
127.2
126.9
123.8
118.0
49.1
44.5
24.6
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

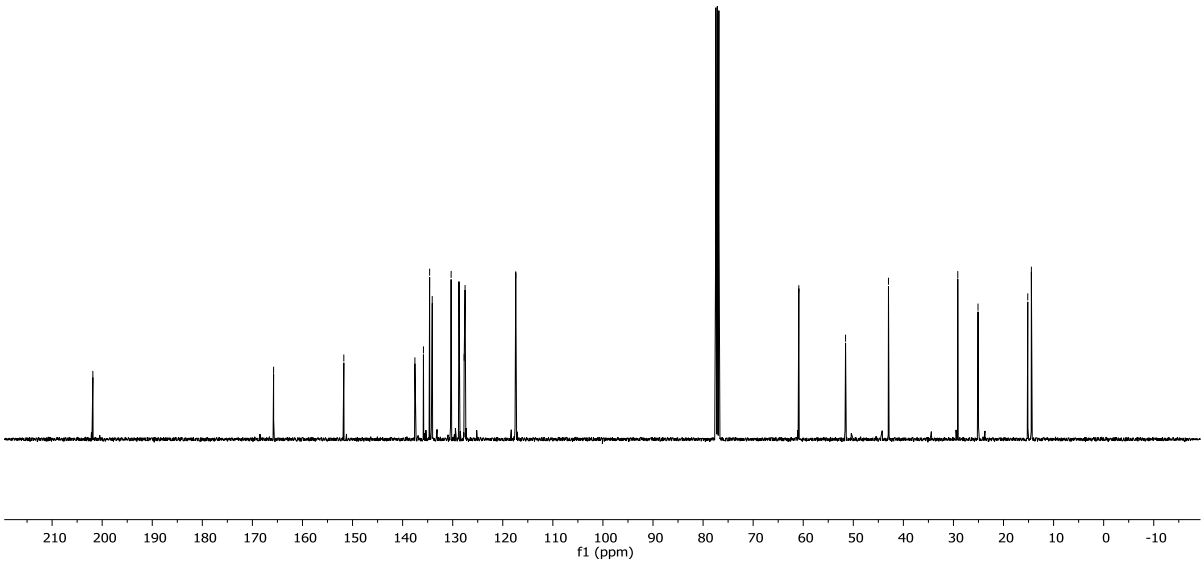


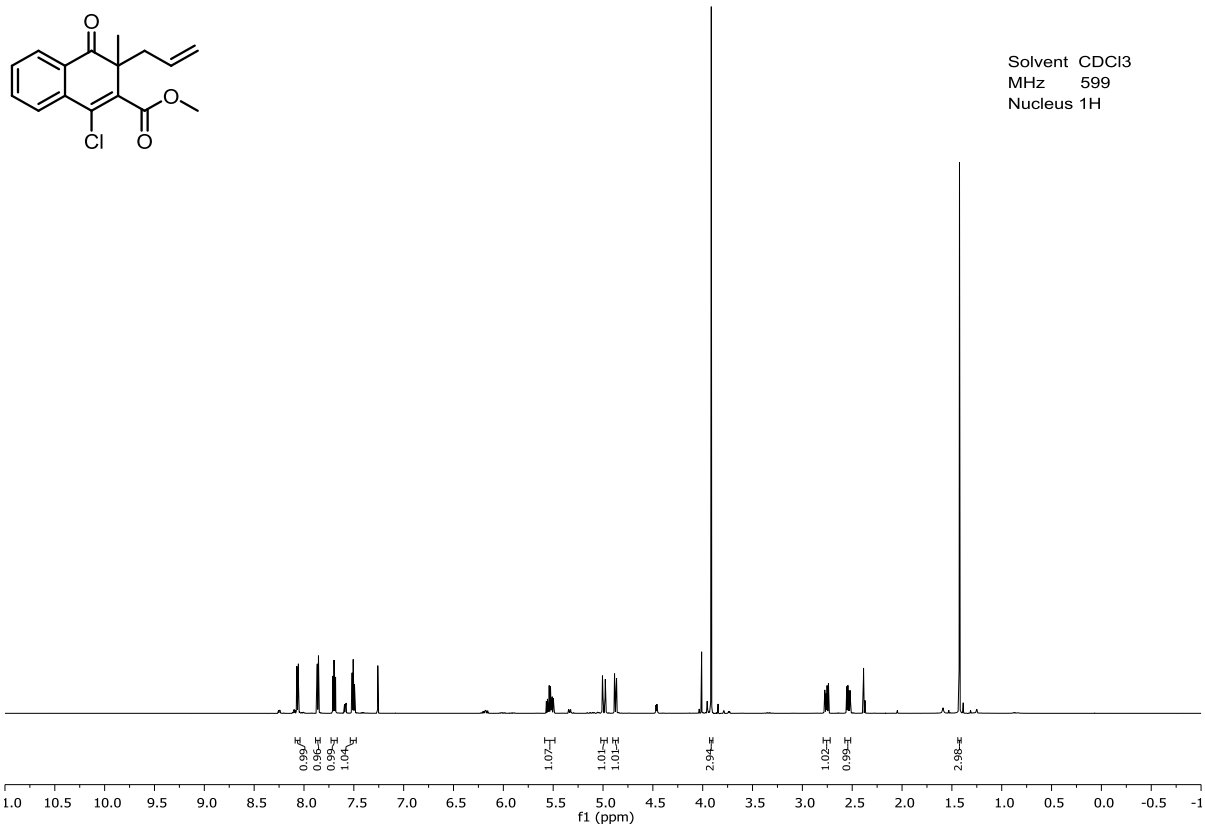
Solvent CDCl3
MHz 400
Nucleus 1H

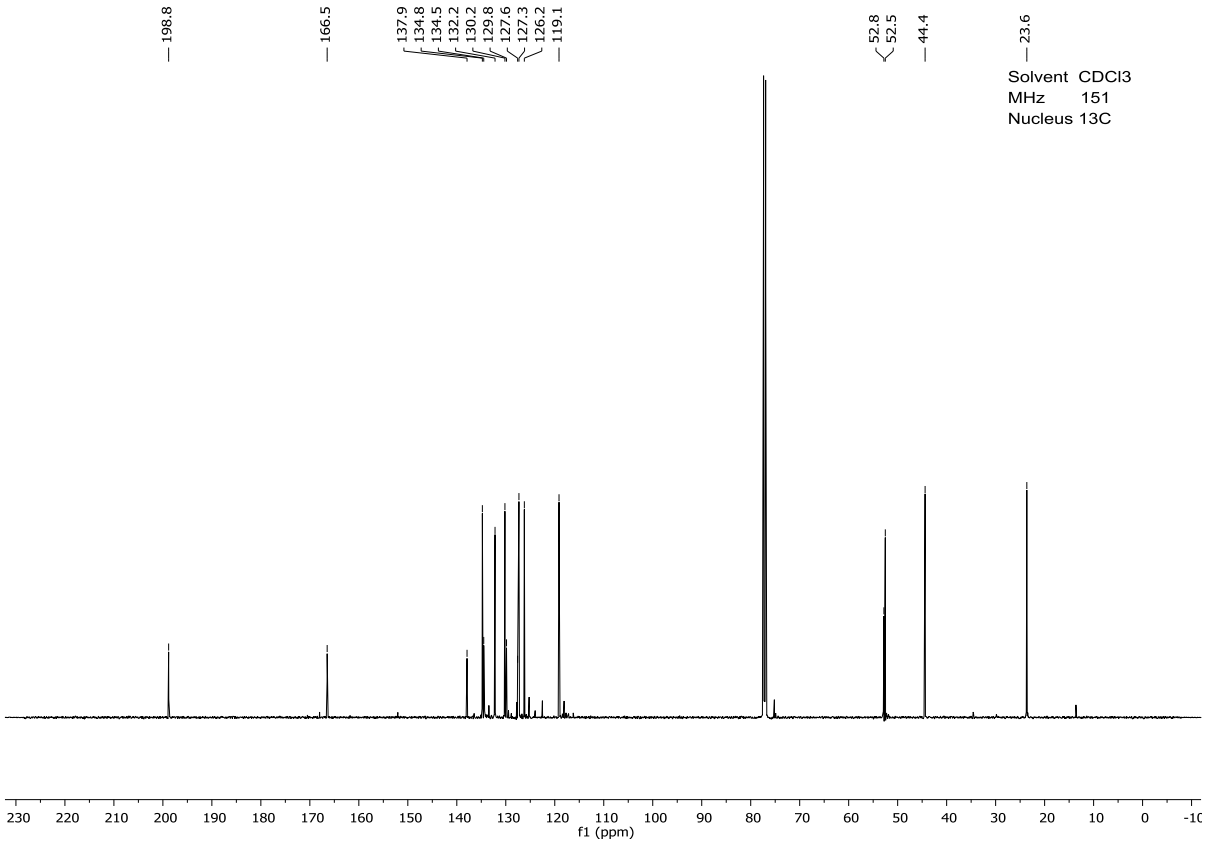


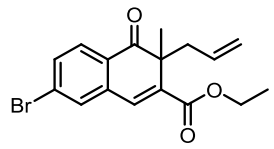
201.9
165.8
151.7
137.5
135.8
134.6
134.1
130.3
128.7
127.7
127.5
117.4
60.9
51.5
43.0
29.1
25.1
15.2
14.4

Solvent CDCl3
MHz 101
Nucleus 13C

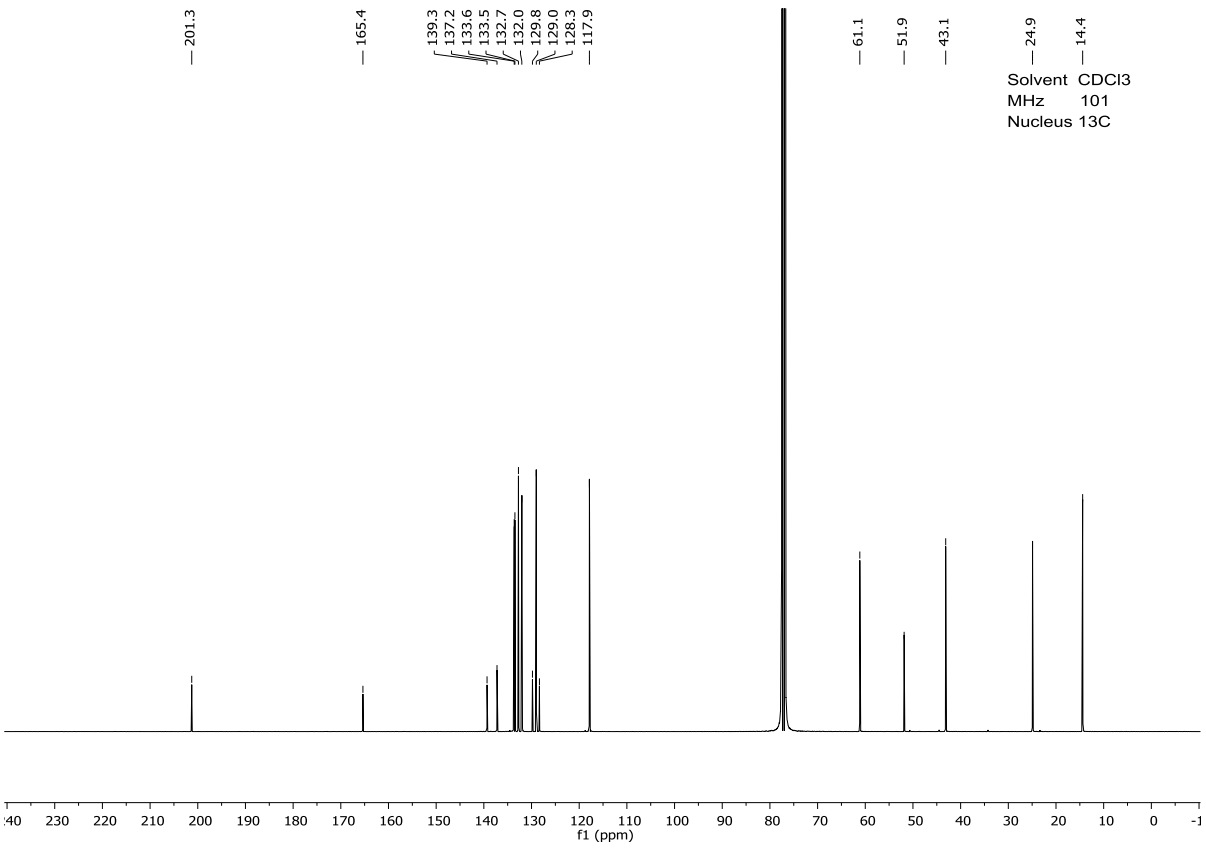



O
O
O
Cl
Solvent CDCl3
MHz 599
Nucleus 1H
0.99
0.96
0.99
1.04
1.07
1.01
1.01
2.94
1.02
0.99
2.98
f1 (ppm)

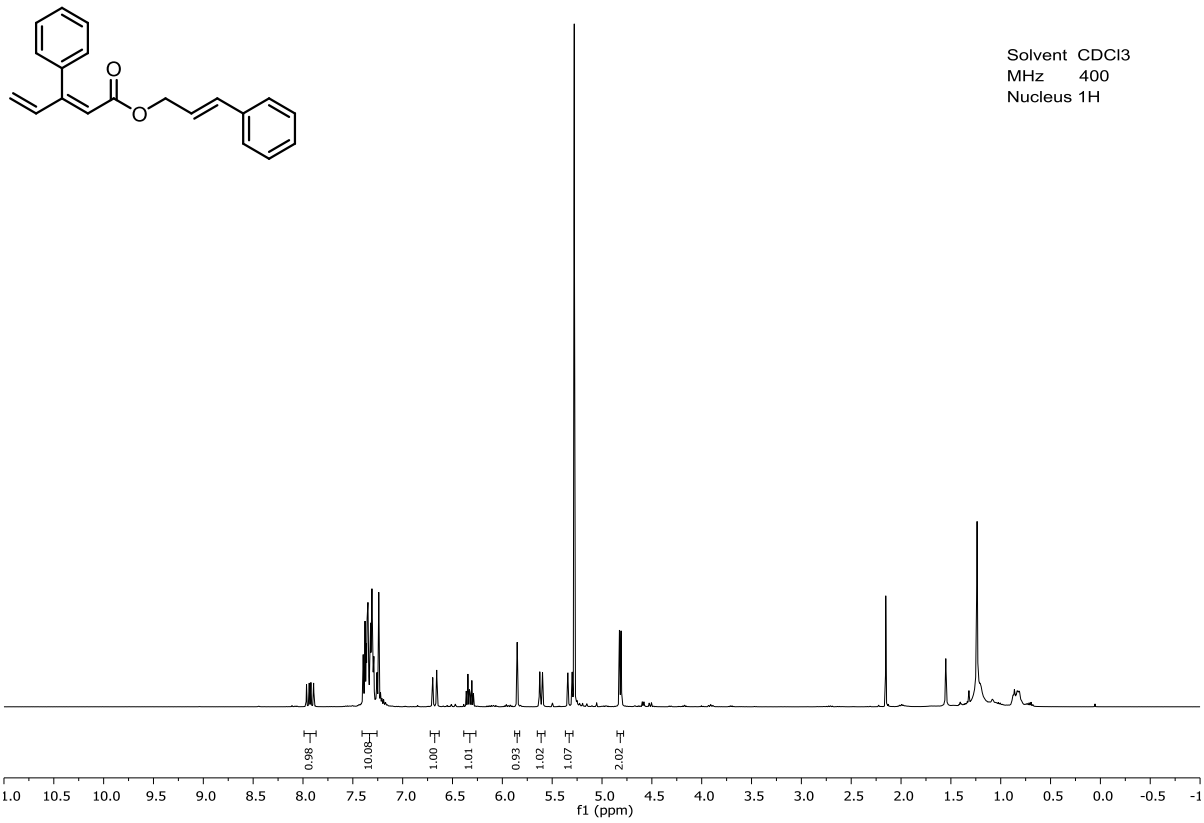

198.8
166.5
137.9
134.8
134.5
132.2
130.2
129.8
127.6
127.3
126.2
119.1
52.8
52.5
44.4
23.6
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)

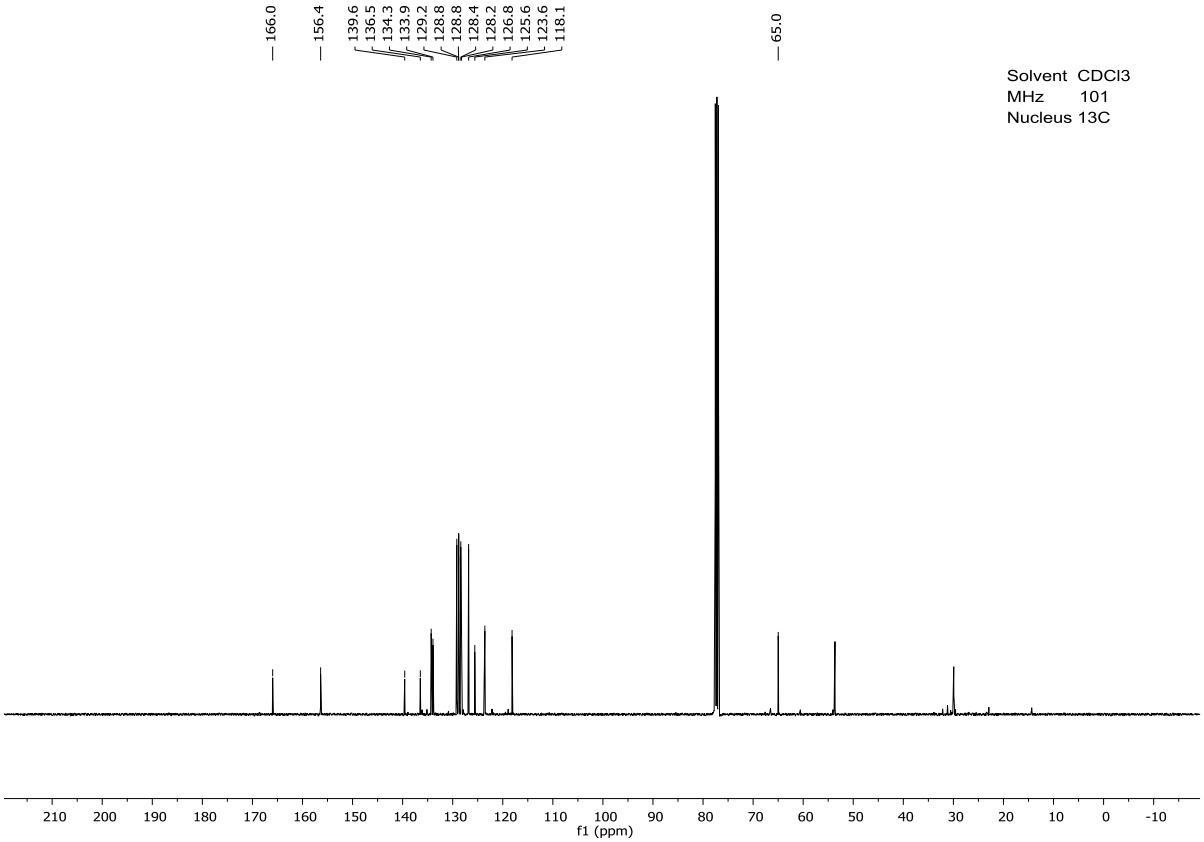

O
Br
O
O

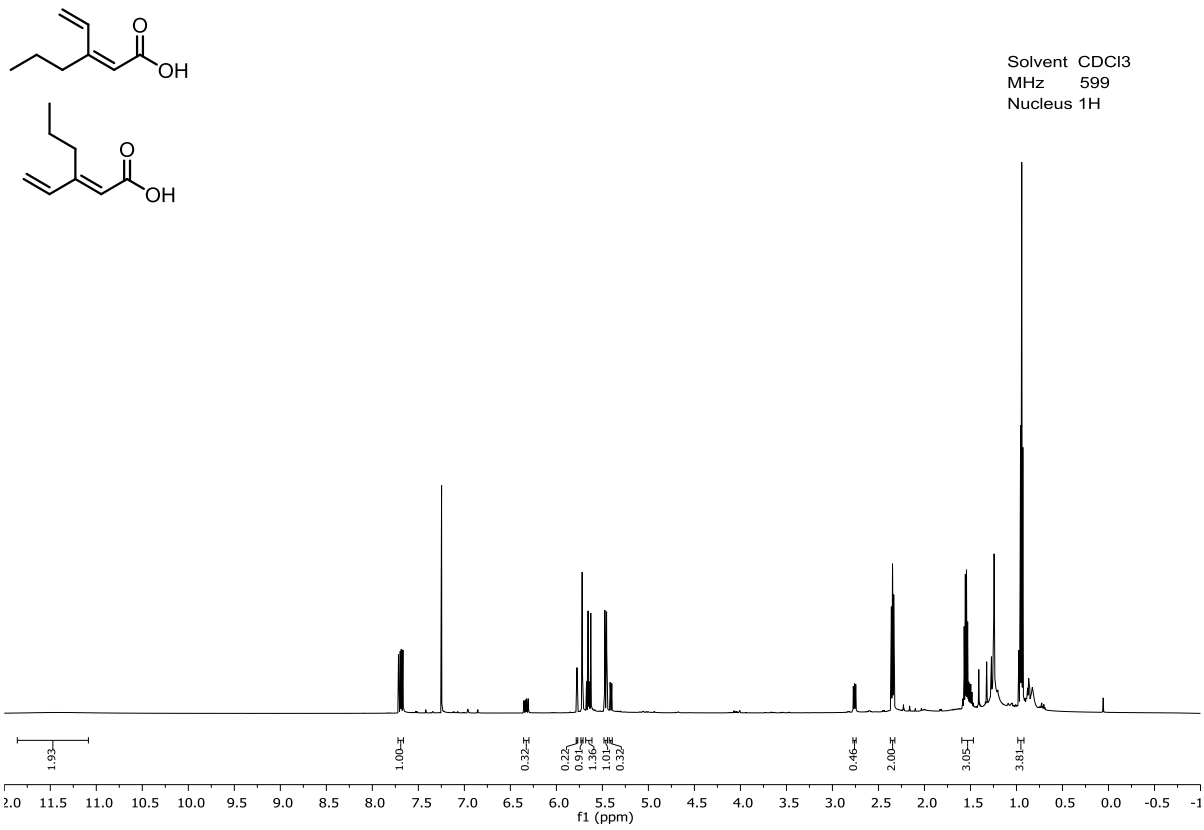
Solvent CDCl3
MHz 400
Nucleus 1H
0.90
0.96
1.00
0.94
1.00
0.98
1.04
1.98
1.03
1.14
2.94
3.10
f1 (ppm)

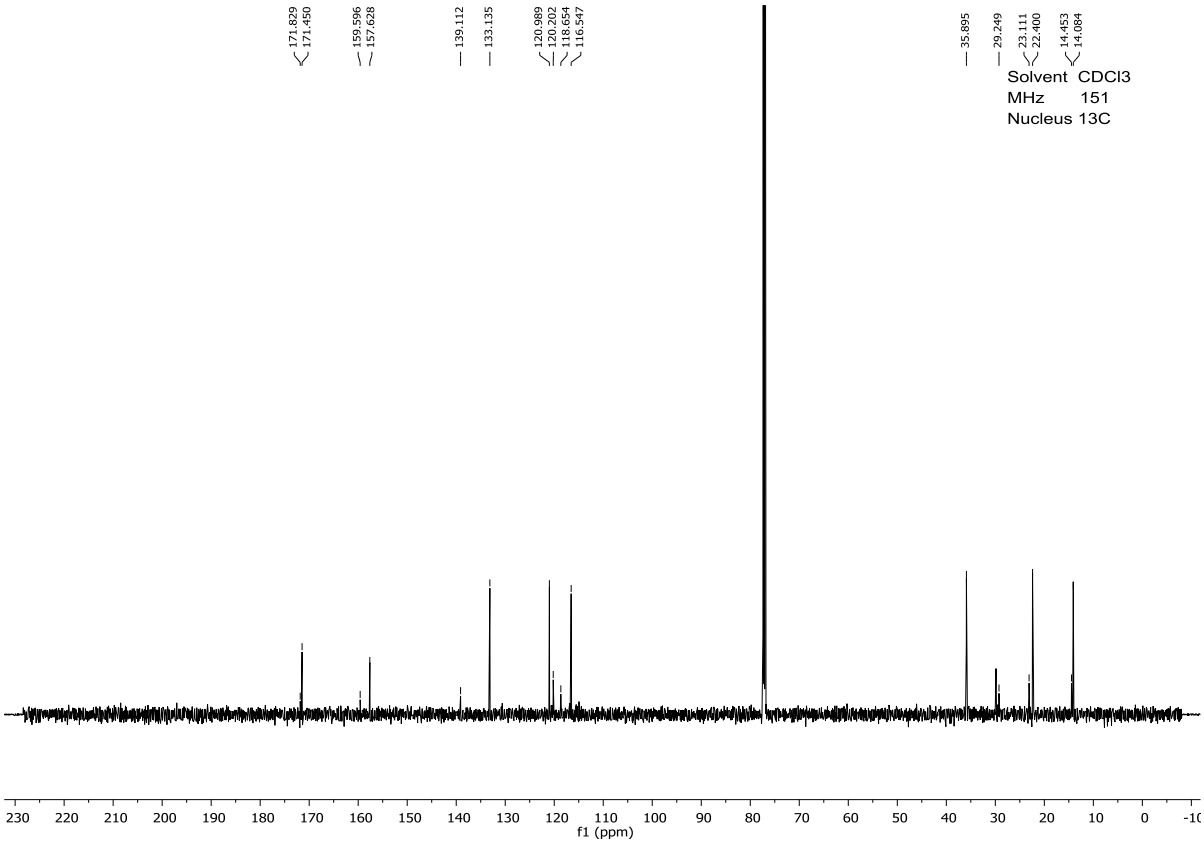

201.3
165.4
139.3
137.2
133.6
133.5
132.7
132.0
129.8
129.0
128.3
117.9
61.1
51.9
43.1
24.9
14.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

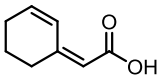
11.4 NMR Spectra of Chapter III

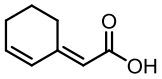




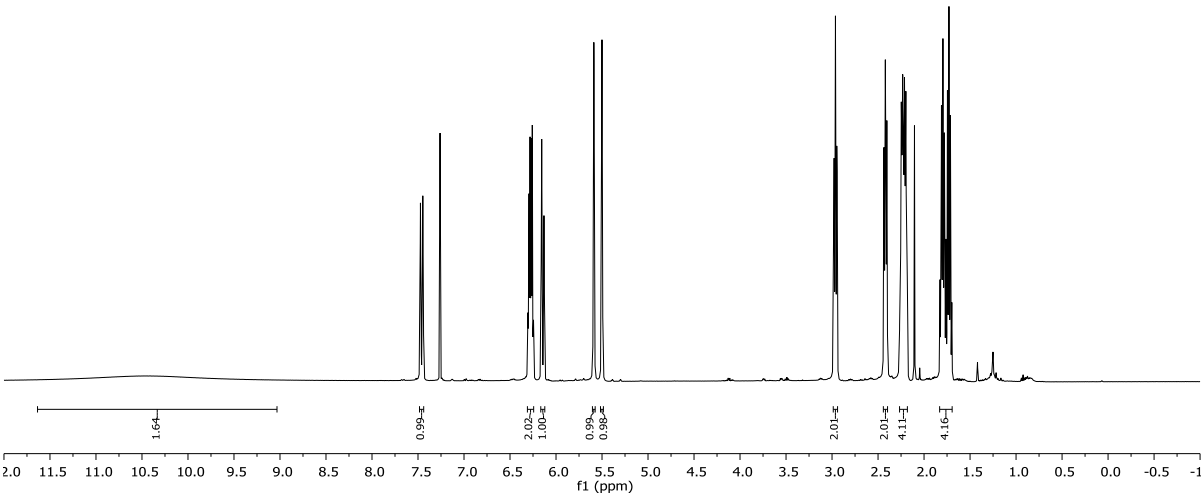

O
OH
O
OH
Solvent CDCl3
MHz 599
Nucleus 1H
1.93
1.00
0.32
0.22
0.91
1.36
1.01
0.32
0.46
2.00
3.05
3.81
f1 (ppm)


171.829
171.450
159.596
157.628
139.112
133.135
120.989
120.202
118.654
116.547
35.895
29.249
23.111
22.400
14.453
14.084
Solvent CDCl3
MHz 151
Nucleus 13C
f1 (ppm)



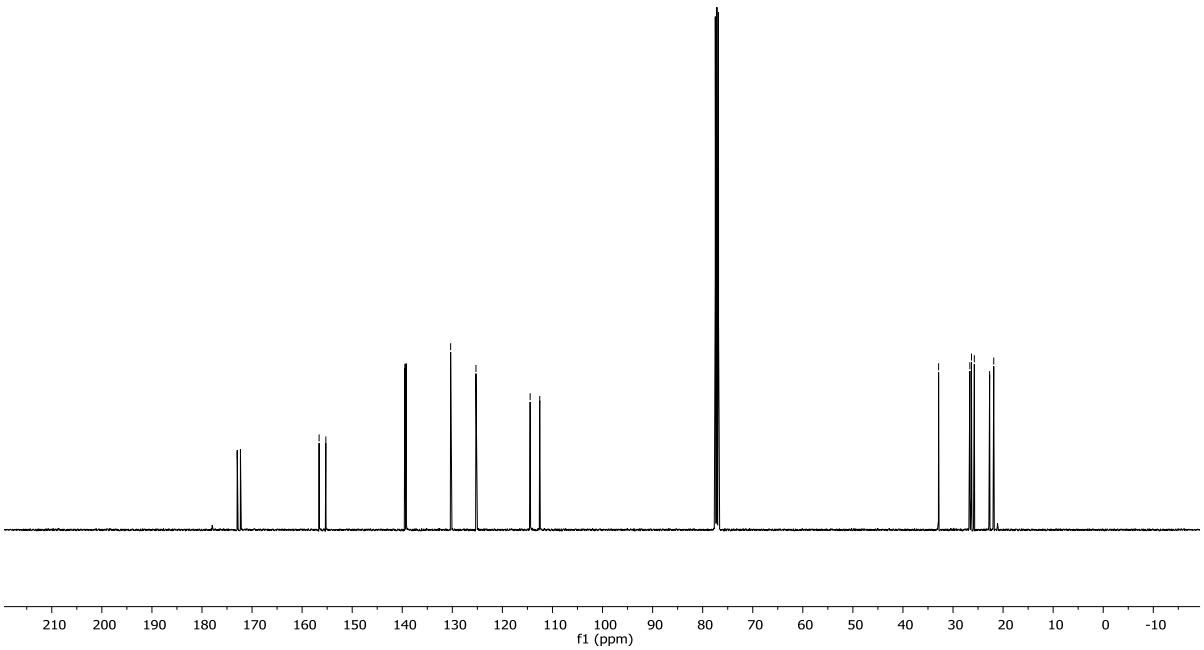


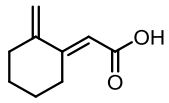
Solvent CDCl3
MHz 400
Nucleus 1H



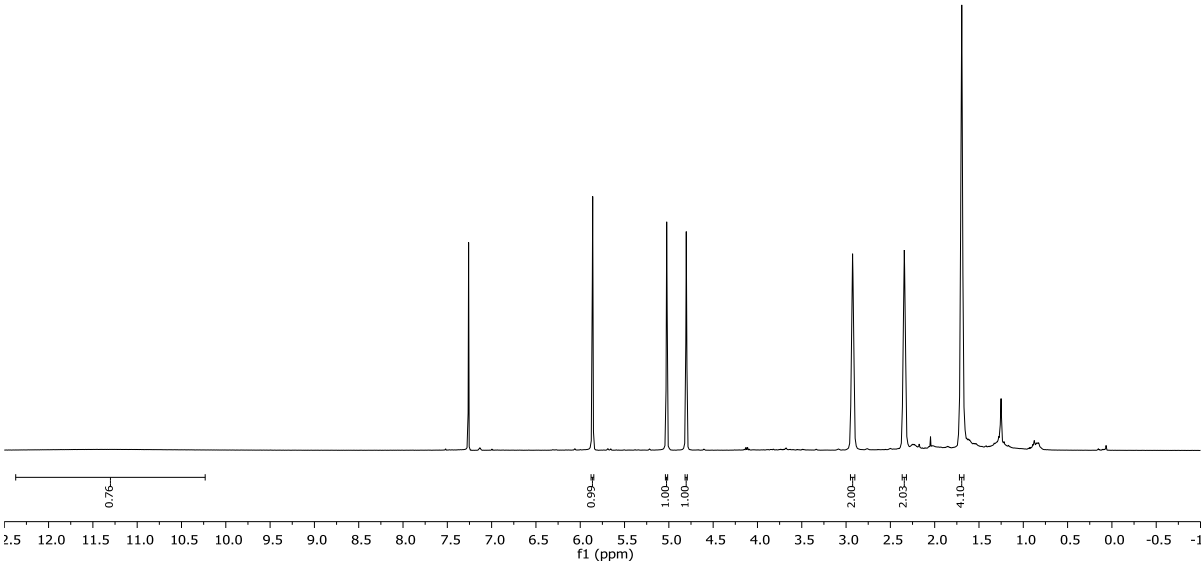
173.0
172.3
156.6
155.3
139.5
139.2
130.3
125.3
114.5
112.5
32.9
26.6
26.3
25.7
22.7
21.9

Solvent CDCl3
MHz 101
Nucleus 13C



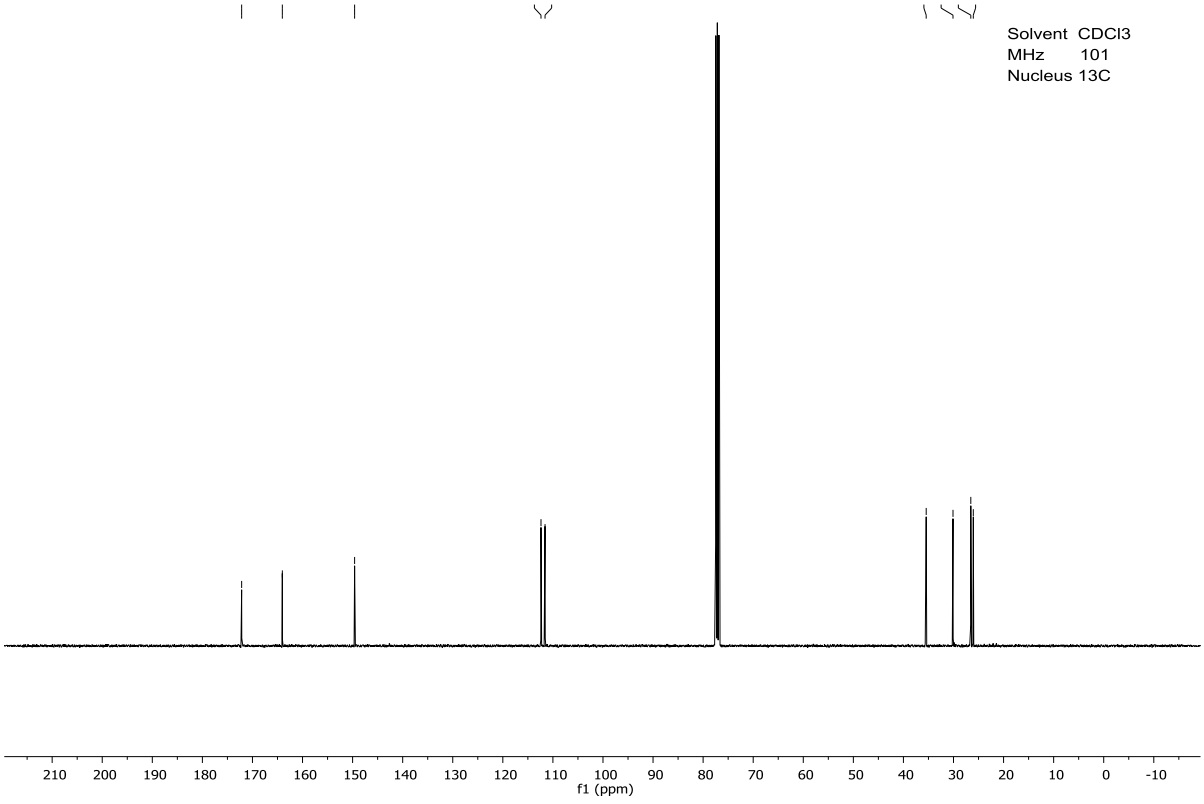


Solvent CDCl3
MHz 400
Nucleus 1H



172.2
164.0
149.6
112.4
111.6
35.5
30.1
26.5
26.0

Solvent CDCl3
MHz 101
Nucleus 13C



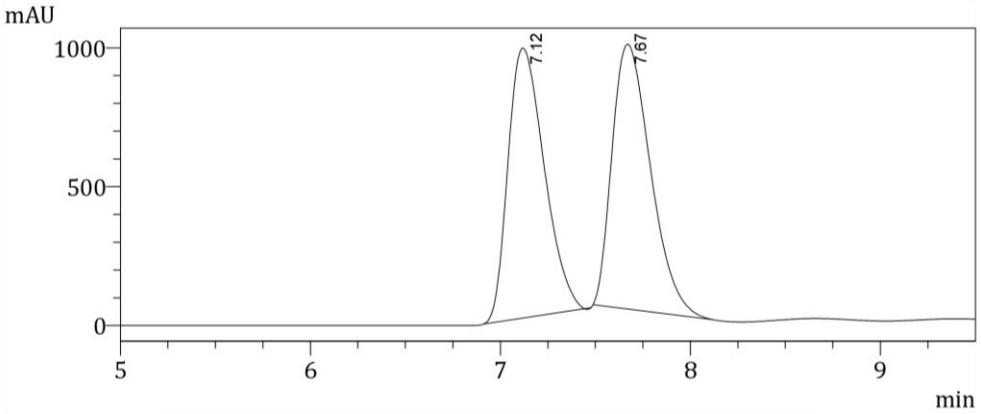
11.5 Chiral HPLC Data

Chiral HPLC of racemic **II.90**:

SHIMADZU LabSolutions Analysis Report

<Sample Information>

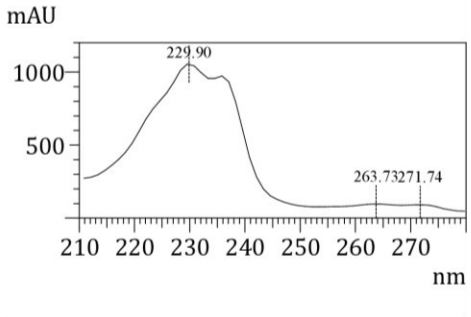
Sample Name	: groa_1333
Sample ID	: groa_1333
Data Filename	: ipa-C5-OBH-100HEPT-30min_40C.lcd
Method Filename	: Adri_C5-OB-H-100-Hept-fl-1-30min-oven-40C.lcm
Batch Filename	: 29_3_2017.lcb
Injection Volume	: 5 uL
Date Acquired	: 29/03/2017 17:42:13
Date Processed	: 30/03/2017 16:30:39



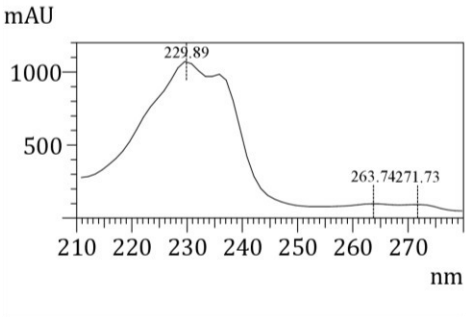
PDA Ch3 230nm

Peak#	Ret. Time	Area	Height	Area%
1	7.12	12911711	972642	49.035
2	7.67	13420003	954532	50.965
Total		26331714	1927174	100.000

UV Spectrum
Peak#: 1
Retention Time: 7.118 min



UV Spectrum
Peak#: 2
Retention Time: 7.670 min

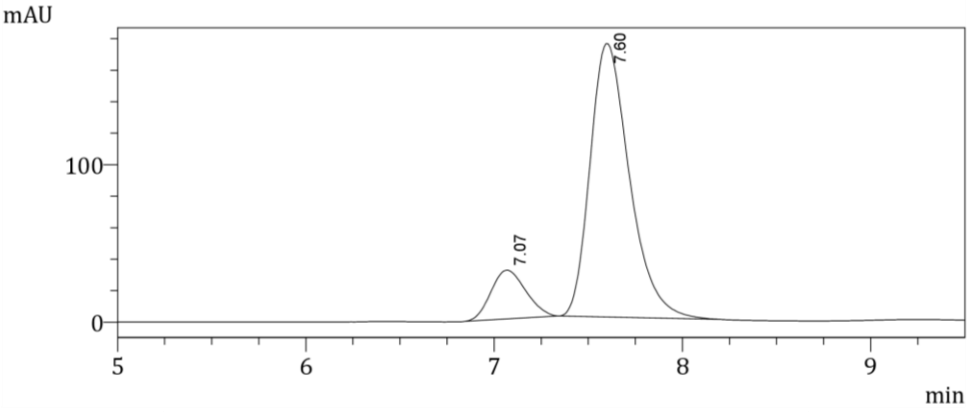


Example of a chiral HPLC analysis of **II.90** synthesized with (*S*,*S*)-DACH-naphthyl Trost ligand ((*S*,*S*)-**L7**):

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

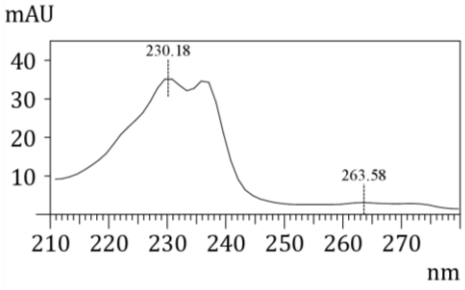
Sample Name	: groa_1347
Sample ID	: groa_1347
Data Filename	: groa_1347_100hept15min40C.lcd
Method Filename	: Adri_C5-OB-H-100-Hept-fl-1-15min-oven-40C.lcm
Batch Filename	: Batch2_05_Apr_2017.lcb
Injection Volume	: 1 uL
Date Acquired	: 05/04/2017 18:24:40
Date Processed	: 05/04/2017 18:39:39



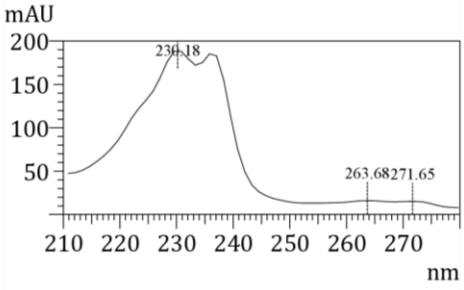
PDA Ch3 230nm

Peak#	Ret. Time	Area	Height	Area%
1	7.07	397706	30953	13.581
2	7.60	2530604	173783	86.419
Total		2928310	204736	100.000

UV Spectrum
Peak#: 1
Retention Time: 7.068 min



UV Spectrum
Peak#: 2
Retention Time: 7.599 min

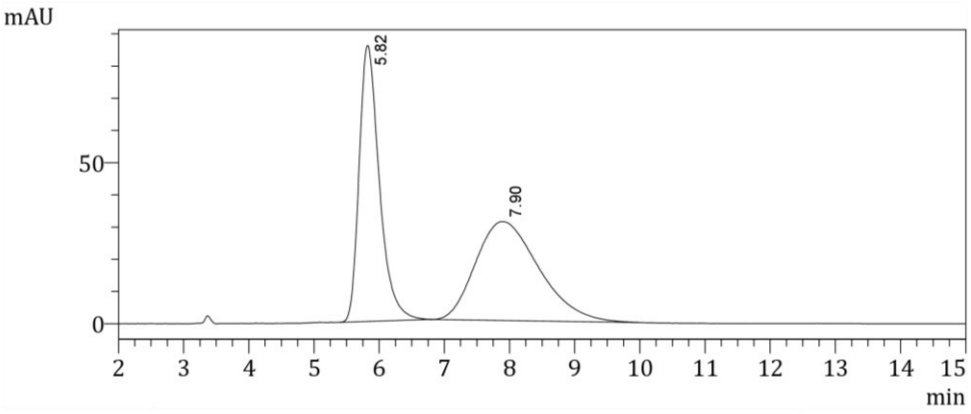


Chiral HPLC of **I.105** :

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: groa_1369
Sample ID	: groa_1369
Data Filename	: groa_1369_90heptMTBE60min40C.lcd
Method Filename	: Adri_C5-OB-H-90-HeptMTBE-fl-1-60min-oven-40C.lcm
Batch Filename	: Batch2_24_May_2017.lcb
Injection Volume	: 5 uL
Date Acquired	: 24/05/2017 21:43:00
Date Processed	: 31/05/2017 09:56:25

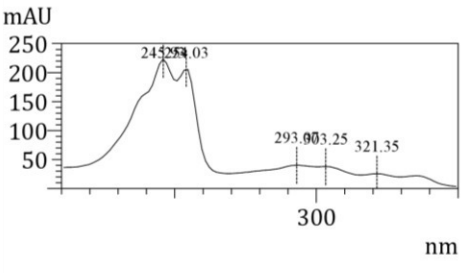


PDA Ch3 230nm

Peak#	Ret. Time	Area	Height	Area%
1	5.82	1849053	85715	47.128
2	7.90	2074443	30712	52.872
Total		3923497	116428	100.000

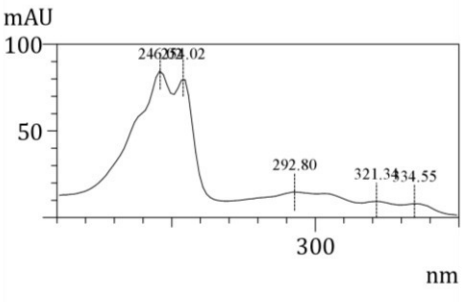
UV Spectrum

Peak#: 1
Retention Time: 5.824 min



UV Spectrum

Peak#: 2
Retention Time: 7.895 min

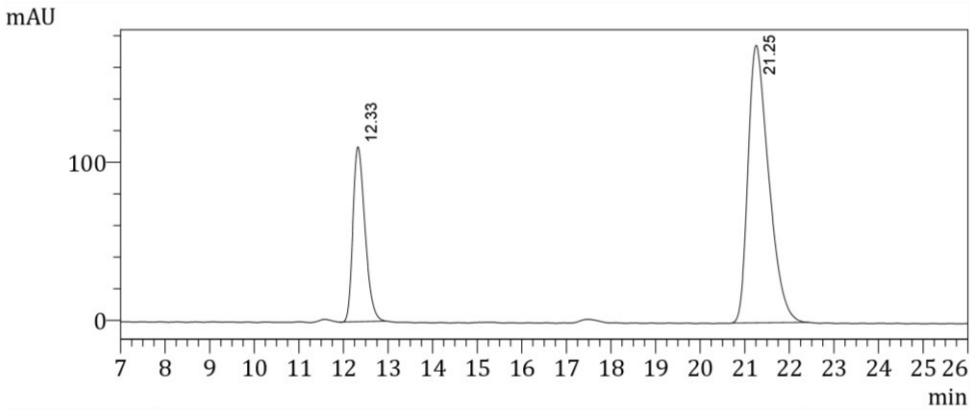


Chiral HPLC of **II.95**:

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: groa_1368
Sample ID	: groa_1368
Data Filename	: groa_1368_95heptMTBE30min40C_ODH.lcd
Method Filename	: Adri_C3-OD-H-95-HeptMTBE-fl-1-30min-oven-40C.lcm
Batch Filename	: Batch2_07_Jun_2017.lcb
Injection Volume	: 5 uL
Date Acquired	: 08/06/2017 10:11:02
Date Processed	: 08/06/2017 10:41:05

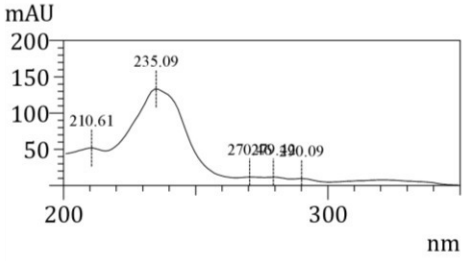


PDA Ch3 230nm

Peak#	Ret. Time	Area	Height	Area%
1	12.33	2079444	110496	26.829
2	21.25	5671397	175517	73.171
Total		7750841	286013	100.000

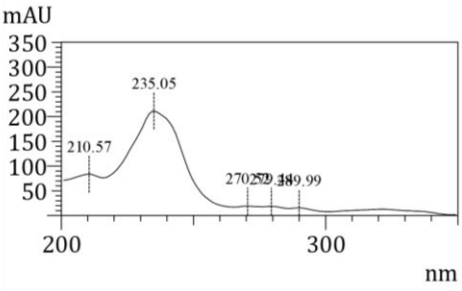
UV Spectrum

Peak#: 1
Retention Time: 12.327 min



UV Spectrum

Peak#: 2
Retention Time: 21.255 min

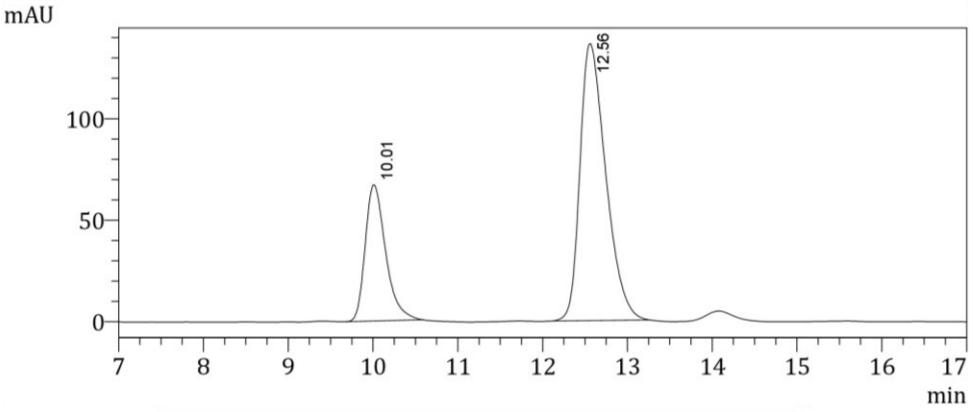


Chiral HPLC of **I.89**:

SHIMADZU LabSolutions Analysis Report

<Sample Information>

Sample Name	: groa_1380
Sample ID	: grpa_1380
Data Filename	: groa_1380_95heptMTBE30min40C_ODH.lcd
Method Filename	: Adri_C3-OD-H-95-HeptMTBE-fl-1-30min-oven-40C.lcm
Batch Filename	: Batch2_07_Jun_2017.lcb
Injection Volume	: 5 uL
Date Acquired	: 08/06/2017 10:41:29
Date Processed	: 08/06/2017 11:11:31



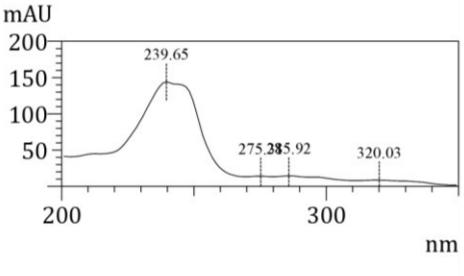
PDA Ch3 254nm

Peak#	Ret. Time	Area	Height	Area%
1	10.01	1125370	67101	27.989
2	12.56	2895423	136496	72.011
Total		4020793	203597	100.000

UV Spectrum

Peak#: 1

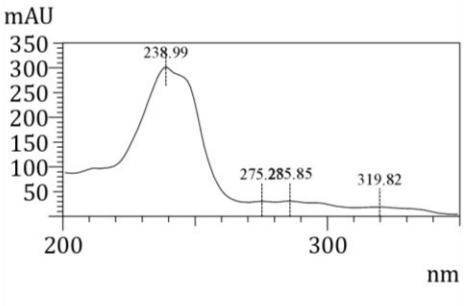
Retention Time: 10.010 min



UV Spectrum

Peak#: 2

Retention Time: 12.560 min



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